ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN

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BY

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(MAY, 2021)

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TO

MY

FAMILY

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ABSTRACT

Introduction: Heart failure is a major global health issue with many recent advances. A new emerging therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed- Angiotensin receptor neprilysin inhibitor (ARNI) which have been shown to improve survival in patients with HFrEF.

Aim of Study: To study effects of SACUBITRIL/VALSARTAN therapy on clinical parameters and echocardiographic features in HFrEF patients switched from angiotensin receptor blockers.

Materials & Methods: A single center, prospective study on HFrEF patients (n=100) meeting inclusion and exclusion criteria's and on ARBs (valsartan/losartan) in addition to optimal medical therapy were included. Data was collected and statistically analyzed at baseline, 6 months and at 1 year for NYHA Functional class, 6 minute walk test and echocardiographic parameters.

Observations- 100 patients with Mean age 61.67±10.47 years and with median duration of heart failure of 25.5(11-44.5) months on optimal therapy with ARBs were included out of which 6 died and 94 were assessed at 6 months which showed no significant improvement in 6 MWDT and echocardiographic remodeling parameters between baseline and 6 months except improvement in NYHA functional class. 26 out of 94 patients selected to switch over to ARNI. During follow up from 6-12 months, 1 out of 26 patients died in ARNI group, 1 patient died and 4 patients (out of 68) lost to follow up due to pandemic situation in ARB group and 88 out of 100 patients completed the study. On comparing ARNI Group (n=25) with ARB group (n=63) we observed significant improvement (*p* values >.05) in ARNI group - 6MWDT by 87.32± 36.96 m, NYHA functional class, EF by 4.6±5.54%, reduction in LVIDs by 2.92± 2.89 mm, reduction in LVIDd by 2.80±6.94 mm, reduction in LA diameter by 3.42±7.13 mm, fall in PASP by 4.12±9.02 mmHg, increase in TAPSE by 2.68±0.84 mm and decrease in MR severity but there was no significant improvement in diastolic function. Regarding adverse effects we found no significant difference in frequency of renal dysfunction, hyperkalemia, hospitalistion rates and mortality in both groups.

Conclusion: Symptomatic HFrEF patients on optimal medical therapy benefits from switching to sacubitril/valsartan from ARB in terms of improvement in NYHA functional class, 6MWD and cardiac reverse remodeling parameters except diastolic function with equal incidences of renal dysfunction, hyperkalemia, hospitalization or mortality rate in both groups.

Keywords- HFrEF, ARNI, SACUBITRIL/VALSARTAN, NYHA, 6MWD

ABBREVATIONS

AF	Atrial fibrillation
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
BNP	Brain natriuretic peptide
ANP	A-type natriuretic peptide
MRAs	Mineralocorticoid receptor antagonists
ARNI	Angiotensin Receptor Neprilysin Inhibitor
NP	Neprilysin
BB	Beta-blocker
CHF	Chronic heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CHD	Congenital heart disease
CAD	Coronary Artery Disease
CHF	Congestive heart failure
CKD	Chronic Kidney Disease
RHD	Rheumatic Heart Disease
VHD	Valvular heart disease
DM	Diabetes Mellitus
HTN	Hypertension
DCM	Dilated cardiomyopathy
IHD	Ischemic Heart Disease
HF	Heart Failure
LVEF	Left ventricular ejection fraction
HFpEF	Heart Failure with Preserved ejection fraction
HFrEF	Heart Failure with reduced ejection fraction
CRT	Cardiac Resynchronization Therapy
ICD	Implantable Cardioverter Defibrillator
VAD	Ventricular Assist Devices

NT-pro-BNP	N-terminal pro-BNP
NYHA	Newyork Heart association
QoL	Quality of Life
6MWT	6 Minute walk Test
AHA	America Heart Association
MR	Mitral Regurgitation
COR	Class of Recommendation
LOR	Level of Evidence
ADHF	Acute decompensated heart failure
GLS	Global longitudinal strain
GCS	Global circumferential strain
S/V	Sacubitril/valsartan
LVIDs	Left ventricular internal diameter in systole
LVIDd	Left ventricular internal diameter in diastole
LA	Left atrium
TAPSE	Tricuspid annular plane systolic excursion
PASP	Pulmonary artery systolic pressure

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INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural and functional defects in cardiac muscle leading to impairment of chamber filling or the ejection of blood. The foremost common cause for HF is reduced left ventricular myocardial function; however, dysfunction of the pericardium, myocardium, endocardium, heart valves or great vessels alone or in combination is also associated with HF. A number of key infective mechanisms leading to HF are increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neuro-humoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis and genetic mutations [1].

As the heart failure advances, it causes a decline in oxidative capacity of skeletal muscle along with reduced capillary density and cross sectional area of myocardial fibre [2,3]. This deranged anatomy of muscular structure and metabolic function sends up in decreased exercise tolerance with increase in morbidity and mortality[4,5] .

The main nomenclature used to describe HF is historical and is predicated on measurement of the LVEF. HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40–49% represent a ‘grey area’, which we now define as HFmrEF. Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, co-morbidities and response to therapies [6].

The burden of heart failure is increasing at an alarming rate in developed and developing countries [7].Heart failure is associated with poor quality of life, shorter life expectancy, and increase frequency of hospitalization causing a major socio economic impact on patient as well as healthcare system.

According to various Indian data and registry [8-13], the mean age of the affected population in India is ranging between 56 years to 61.2 years affecting male gender (62-83%) as compared to female gender.

There are multiple etiologies associated with heart failure like coronary artery disease (ischemic heart disease), dilated cardiomyopathy, rheumatic heart disease (RHD), hypertensive heart disease, valvular heart disease out of which the most common being coronary artery disease (ischemic artery disease) the mean percentage ranging between 37.3% to 76.9% .Similarly there are numerous associated co morbidities associated with heart failure for instance hypertension, diabetes mellitus (DM), chronic kidney disease, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD) atrial flutter, atrial fibrillation. The comorbidities play a vital role in deciding overall prognosis including morbidity and mortality of the patient. Different Indian data and registry mention the most common associated comorbidity being Hypertension (37% to 58%) then diabetes mellitus (23% to 48.8%).Hence the overall incidence is likely to increase if the following factors are associated like aging population, risk of coronary artery disease prevalence, epidemic increment of comorbidities being most common hypertension and diabetes mellitus and persistence of rheumatic heart disease and any untreated congenital heart disease (CHD) [11,14,15,16] .

Heart failure has apparently become a major global health issue with an approximated global prevalence of more than 37.7 million [17]. Data shows that the mortality rate is around 50% at 5 years from the initial diagnosis of heart failure [18].HF is a leading cause of hospitalization and represents 1–5% of total hospital admissions [17,19,20]. About 2–17% of HF patients admitted to hospital die while in the hospital [3]. Patients who survive have a high rate of rehospitalization and poor QoL [2,19]. Despite improvements in medical care over the years, the prognosis of patients with HF remains poor and the survival rate is worse than in those with breast, bowel or prostate cancer [19].

The current estimate regarding incidence of heart failure in India ranges in between 1.3 to 2.3 million[8]. The Trivandrum Heart Failure Registry (THFR) reported that HF with preserved ejection fraction accounted for 25% of the total heart failure burden. The prognosis of HF in Indian patients appears to be worse than those in the West. The in-hospital mortality observed in the THFR (8.4%) was almost double compared to that reported in the ADHERE registry (4%) of the USA. The INTER-CHF study also showed that the 1-year mortality of HF is high in India i.e., 37%. As HF presents about a decade earlier in Indians, it generally affects the patients in the crucial stage of their lives. Majority of the Indian patients are from low socio-economic strata, who have to spend out-of-pocket for their treatment, unlike in the West.

It is always aimed to initiate an appropriate treatment intending for better outcome of the patient in terms of reduction in morbidity and mortality, hospitalization duration, and health care cost. However, the diagnosis and high risk stratification of the patient is exigent at times. All of the patients do not exhibit typical symptoms and neither do all patients who give the impression of typical symptoms have heart failure. Therefore, it is of great magnitude and concern that there should be an accurate diagnostic tool for evaluation and high risk stratification of the patient for prompt initiate of treatment. Identification should be the key aspect for accurate diagnosis to surpass the known consequences of heart failure. There are various pharmacological and non-pharmacological modalities for the treatment of heart failure at present. The pharmacological treatment modalities includes various drugs including Angiotensin converting enzyme inhibitors (ACEI), Angiotensin II receptor blockers (ARBs), Beta blockers, Diuretics, angiotensin receptor neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonist (MRAs),Funny channel inhibitors like ivabradine. The Non Pharmacological treatment includes devices like implantable cardioverter defibrillators (ICD), cardiac resynchronization therapy (CRT), and ventricular assist device (VAD).

Neuro-hormonal antagonists (ACEIs or ARBs, MRAs and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (SACUBITRIL/VALSARTAN)]. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. The degradation of NPs, bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodeling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy[21].The new joint guidelines from the American College of Cardiology, American Heart Association, and Heart Failure Society of America advocate sacubitril/valsartan for patients with HFrEF who have symptoms that meet New York Heart Association class II or III heart failure and can tolerate an ACE inhibitor or ARB. Even further, these guidelines recommend replacing ACE inhibitor or ARB therapy with sacubitril/valsartan in patients with adequate blood pressure for morbidity and mortality benefit [22].

Oral bioavailability of LCZ696 is >=60%.Steady-state is reached in 3 days. It is highly protein bound 94-97%.Volume of distribution is 75 L for sacubitril and 103 L for valsartan. Sacubitril component is primarily excreted in the urine (52-68%) and stool (37-48%). Valsartan component is primarily excreted in the stool (86%) and to a lesser extent in the urine (13%). Despite the superiority of sacubitril/valsartan over enalapril in the PARADIGM-HF trial, some relevant safety issues remain when initiating treatment with this drug in clinical practice. Symptomatic hypotension was

more often present in the sacubitril/valsartan group although there was no increase in the rate of discontinuation. Sacubitril/valsartan tends to increase risk of angioedema. If angioedema occurs, sacubitril/valsartan should be discontinued and should not be rechallenged. Sacubitril/valsartan should not be used in those with a history of angioedema related to previous ACE inhibitor or ARB therapy. If switching to or from an ACEi or ARB, a 36-hour washout period is required between drugs. Combined treatment with an ACEI (or ARB) and sacubitril/valsartan is contraindicated. Being a RAAS blocking agent; LCZ696 (sacubitril/valsartan) may cause impaired renal function in high risk individuals including those with renal artery stenosis. Because of RAAS blockade, sacubitril/valsartan may cause hyperkalemia. There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition [23].

AIMS AND OBJECTIVES OF THE STUDY

- To study clinical and echocardiographic features in systolic heart failure patients on Angiotensin receptor blockers.
- Assessment of clinical and echocardiographic features when patients were switched over from Angiotensin receptor blockers to SACUBITRIL/ VALSARTAN therapy and comparison between two groups.

REVIEW OF LITERATURE

Heart failure (HF) is an important clinical syndrome associated with emergency admissions, morbidity, readmissions and mortality. Pathophysiology of HF includes structural and functional alterations of cardiac muscle, activation of renin-angiotensin system (RAS). Stimulation of RAS initially helps to augment blood pressure and cardiac contractility, but overtime becomes counterproductive and causes worsening of HF by fluid retention. The management of HF is based on our understanding of these mechanisms and the mainstay of pharmacotherapy includes diuretics, β blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB). The latter drugs have been the cornerstone of therapy of HF over the last two decades. Apart from RAS, other neurohormonal substances are also implicated in the pathophysiology of HF.

De Bold *et al.* have reported that intravenous injection of atrial muscle extract produced a rapid; 30-fold natriuretic response in rats [24]. This led to the discovery of natriuretic peptides (NPs), small peptide hormones predominantly secreted by the cardiac myocytes in response to stretching forces. Currently there are six NPs – atrial NP, brain NP (BNP), C-type NP, dendroaspis NP, ventricular NP and urodilatin [25].

NPs cause natriuresis, vasodilation, possess antiproliferative effects, cause vascular remodeling and modulation of renin–angiotensin–aldosterone systems thus benefiting in treatment of HF. These NPs are degraded majorly by neprilysin, a membrane bound endopeptidase and through a clearance receptor (the NP clearance receptor) [26].

Therapeutically beneficial effects of NPs may be derived by one of the two methods:

1. By exogenous administration of NPs or;
2. By inhibition of their degradation by neprilysin inhibitors.

While exogenous administration is the best possible way to acutely augment NPs action, requirement of intravenous infusion, lack of clinical

efficacy and durable effect are shortcomings of this approach. Two agents nesiritide, a recombinant BNP and carperitide, recombinant atrial NP are examples of this approach.

The second method of augmenting NPs action is by inhibiting neprilysin – in contrast with parenteral administration, three oral drugs – racecadotril, ecadotril [27] and candoxatril were tested. However, these drugs failed to provide sustained hemodynamic benefit. The reason being neprilysin also breaks down angiotensin II and by inhibiting neprilysin, increase in angiotensin II levels occurs. Angiotensin II is a potent vasoconstrictor and offsets the beneficial effects of vasodilation provided by neprilysin. Addition of ACE inhibitors to neprilysin inhibitors helps to balance these opposing effects. One important side effect of ACE inhibitors is increased angio edema due to excess of bradykinin. To overcome this unwanted adverse effect of angio edema, instead of ACE inhibitors, angiotensin receptor blockers were added to neprilysin inhibitors with favorable results, thus ushering in the concept of angiotensin receptor – neprilysin inhibitor (ARNI).

Neprilysin inhibition with ACE inhibition

The first combined angiotensin converting enzyme inhibitor (ACEI) and neprilysin inhibitor developed was omapatrilat, an orally active, long acting, selective, competitive inhibitor of neutral endopeptidase and angiotensin converting enzyme.

Initial clinical study involving 573 patients comparing omapatrilat 40 mg (n = 289) with lisinopril 20 mg (n = 284) in patients with HF, IMPRESS randomized trial, suggested a trend toward benefit on the combined end point of death or admission for worsening HF (p = 0.052; hazard ratio: 0・53) [28] . Further strength to this drug was gained by another large, randomized clinical study involving 5770 patients with moderate-to-severe HF randomized to omapatrilat 40 mg daily (n = 2886) and enalapril 10 mg twice daily (n = 2884), in OVERTURE trial [29], showed omapatrilat-reduced morbidity and mortality but was not more effective than ACE

inhibition alone in reducing the risk of the combined risk of death or hospitalization for HF requiring intravenous treatment. However, Omapatrilat inhibits aminopeptidase that catabolizes bradykinin, thereby resulting in excess bradykinin, which in turn causes more angioedema [30]. A study assessing the safety and efficacy of omapatrilat in comparison with enalapril in hypertensive patients also showed excess incidence of angioedema with omapatrilat (2.17 vs 0.68%) [31].

Neprilysin inhibition with ARBs

The major shortcoming of omapatrilat, namely the risk of angioedema was surmounted by development of an ARNI, sacubitril-valsartan, known as LCZ696. Soon after oral ingestion, LCZ696 dissociates into sacubitril (a neprilysin inhibitor prodrug, AHU-377, which is enzymatically cleaved to the active form, LBQ657 and valsartan). Valsartan blocks angiotensin II Type 1 receptor, and LBQ657, the active metabolite of sacubitril (AHU377), does not inhibit aminopeptidase P, the risk of angioedema is considered to be less than with omapatrilat. Sacubitril-valsartan is administered twice daily therefore providing sustained Neprilysin and RAAS inhibition over a 24-hperiod addressing one limitation of the OVERTURE trial in which omapatrilat was given as a single large dose once daily [32].

Dose & availability

The dose of sacubitril-valsartan (LCZ696) is 49⁄51 mg (i.e., 100 mg LCZ696) taken per orally twice daily and up titrated to a target dose of 97⁄103 mg (i.e., 200 mg) twice daily. Lower starting dose of sacubitril-valsartan (24⁄26 mg) may be used in selected patients and uptitrated every 3–4 weeks [33]. With the publication of PARADIGM HF trial, ARNI has become an important advance in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF). Encouraged by results of this trial, several other indications in cardiovascular disease (CVD) are being explored.

Heart failure with reduced ejection fraction

PARADIGM-HF [34] trial was a 'game-changer' for the concept of ARNI in treatment of HFrEF. In this large double-blind trial, 8442 patients with class II, III or IV HF and an ejection fraction of 40% or less were randomly assigned to receive LCZ696 at a dose of 200 mg twice daily (n = 4187) or enalapril at a dose of 10 mg twice daily(n = 4212), in addition to recommended therapy. After a median follow-up of 27 months, the trial was stopped due to overwhelming benefit of LCZ696 over enalapril. The study drug LCZ696 proved superior to enalapril in:

• The primary outcome of composite of death from CV causes or hospitalization for HF (21.8 vs. 26.5%; p = 0.001);

• Difference in the rates of death from CV causes 13.3 vs 16.5% (p = 0.001);

• Decreasing the risk of hospitalization for HF by 21 %(p = 0.001).

Apart from these hard end points, the drug also proved to significantly reduce the clinical worsening of patients evidenced by reduction in intensification of medical treatment for HF (520 vs 604; HR: 0.84;p = 0.003) or an emergency department visit for worsening HF (HR: 0.66; p = 0.001) [35].

The beneficial effects were evident as early as 30 days. The superiority of LCZ696 over enalapril was not accompanied by important safety concerns. Fewer patients stopped their study medication overall or because of an adverse event such as symptomatic hypotension or worsening of serum creatinine in the LCZ696 group than in the enalapril group. It helped to establish the safety and efficacy of sacubitril-valsartan over ACE inhibitors. PARADIGM-HF trial was designed to provide evidence to support the replacement of ACE inhibitors or ARBs with LCZ696 in the management of chronic HF and was successful in the same as the 2017 ACC/AHA/HFSA.

Heart Failure Focused Update recommends in patients with chronic symptomatic HFrEF New York Heart Association class II or III who tolerate

an ACE inhibitor or ARB, replacement with an ARNI to further reduce morbidity and mortality is indicated as COR I, LOE – B [36].

A retrospective study was conducted by R. De Vecchis et al in year 2017 aimed to assess the effects of sacubitril/valsartan in addition to a beta-blocker and mineral receptor antagonist (MRA) in a group of HFrEF patients with NYHA class II-III HF vs. conventional therapy (ACE inhibitor or angiotensin II receptor blocker added to a beta-blocker plus an MRA) administered to a control group with comparable clinical features. Both groups patients were on variable doses of diuretics. Mortality at 6 months was 6.8% in patients taking sacubitril/valsartan vs 34% in those on conventional therapy (odds ratio [OR] = 0.14; 95% CI: 0.04-0.49). Moreover, there was a 4.5% rate of HF hospitalizations in the sacubitril/valsartan group vs. 59% in the control group (OR = 0.03; 95% CI: 0.01-0.14). It was concluded that Sacubitril/valsartan offered strong protection against all-cause death and HF hospitalizations at 6 months without any significant side effects [37].

Acute heart failure with reduced ejection fraction

PIONEER-HF study randomized 881 patients with HFrEF who were hospitalized for ADHF and stabilized to receive sacubitril–valsartan (n = 440) or enalapril (n = 441). The medication was started at a lower dose of sacubitril/valsartan (24/26 or 49/51 mg), and for enalapril (2.5 or 5 mg), both given orally twice daily and uptitrated to maximum dose of 97/103 mg twice daily and enalapril to 10 mg twice daily. Eight weeks after discharge, the sacubitril/valsartan group had a 29% greater reduction in NT-proBNP and a 42% lower rate of the composite clinical end point of CV death or HF rehospitalization than the enalapril group [38]. Open label treatment of both groups of PIONEER-HF patients with sacubitril-valsartan to additional 4 weeks, provided additional 36% reduction in NT-proBNP in enalapril-treated patients while maintaining 18.5% reduction in sacubitril-valsartan group. More importantly the relative risk of the composite end point of CV death, HF rehospitalization or LV assist device implantation during the 4-

week extension phase was 33% lower in the continuous sacubitril/valsartan group than in the switchers. These points highlight the safety of initiating sacubitril-valsartan in stabilized ADHF patients.

The safety and tolerability of initiating and uptitrating to maximum dose of ARNI was assessed in HFrEF patients after they have been stabilized following an ADHF episode in TRANSITION study that randomized 991 patients after stabilization to initiate sacubitril/valsartan either ≥12-h predischarge (n = 495) or between days 1–14 post discharge (n = 496) [39]. The proportion of patients who achieved and maintained for ≥2 weeks leading to week 10, either 49/51 or 97/103 mg bid was 62.1% versus 68.5% (p = 0.034); or any dose was 86.0% versus 89.6% (0.089). More than 80% of patients with SBP ≥100 mmHg achieved and maintained the target dose of sacubitril/valsartan if the treatment was titrated gradually; underscoring the need for care in this high risk condition. The incidence of adverse events and discontinuations of ARNI due to adverse events was similar in both groups.

Wachter and colleagues in year 2018 randomly assigned 1,002 patients (mean age 67 years; 75% men; mean LVEF 29%) hospitalized for acute decompensated HF with reduced EF to sacubitril/valsartan after being hemodynamically stabilized while still in the hospital or after discharge. Patients were also stratified based on whether they were already taking an ACE inhibitor, an ARB or neither before hospitalization. Of the cohort, 29% were newly diagnosed with HFrEF and 24% had not previously taken ACE inhibitors or ARBs. The primary endpoint was proportion of patients achieving the target dose of sacubitril/valsartan 200 mg twice daily at 10 weeks after randomization. Secondary endpoints included discontinuation due to adverse events and tolerability of different sacubitril/valsartan doses. The primary endpoint was achieved in 45% of the predischarge group vs 50.4% of the postdischarge group. In addition, 62.5% of the predischarge group and 68% of the postdischarge group maintained a dose of 100 mg or 200 mg for at least 2 weeks leading to week 10 after

randomization, whereas 86.4% of the predischarge group and 88.8% of the postdischarge group maintained any dose for at least 2 weeks leading to week 10 after randomization. Study drug discontinuation occurred in 4.5% of the predischarge group and 3.5% of the postdischarge group. Rates of adverse events, serious adverse events and death did not significantly differ between the groups. So it was concluded that it is safe and efficacious to start sacubitril/valsartan in the hospital setting, whether the patient is on a high dose or a medium dose of the drug [40].

Heart failure with preserved ejection fraction

NT-pro BNP is a marker for diagnosis and prognosis of HF. Reduction in NT-pro BNP levels in patients with LV ejection fraction ≥45% with sacubitril-valsartan was studied in PARAMOUNT trial. 301 patients were randomized to sacubitril-valsartan (n = 149) or valsartan alone (n = 152) and it was found that NT-pro BNP levels significantly decreased in former group ([783 pg/ml at baseline and 605 pg/ml] compared with the latter group [862 pg/ml at baseline and 835 pg/ml] at 12 weeks.) [41]. There was 7% reduction of LA volume (p = 0.003) indicating reverse left atrial remodeling, 9% improvement in New York Heart Association class (p = 0.051).

While PARAMOUNT trial assessed the efficacy of sacubitril-valsartan on the biomarker NT-proBNP, PARAGON HF trial assessed the clinical primary end point of composite of total hospitalizations for HF and death from CV causes in patients with HFpEF. In this study, 4822 patients with HFpEF were randomized to sacubitril-valsartan (n = 2407) and valsartan alone (n = 2389). The study failed to show significant beneficial effect with sacubitril-valsartan [42].

Sacubitril-valsartan in cardiac remodeling

Earliest study of ARNI on cardiac remodeling in HFrEF was published by Martens *et al.*, who prospectively evaluated 125 patients switched from RAS blockers to sacubitril-valsartan [43]. During a median follow-up of 4 months significant improvement in LVEF (29.6 ±6% vs 34.8 ±6%; p <.001)

and decrease in LVESV (147±57 ml vs 129±55 ml; p <.001) and LVEDV (206 ±71 ml vs 197±72 ml; p = .027) was observed. Diastolic function also improved with decrease in E/A-wave ratio (1.75 ±1.13 vs 1.38 ±0.88; p = .002) and drop in the percent of patients with a restrictive mitral filling pattern from 47 to 23% (p = .004).

PROVE HF study assessed the correlation of reduction in NT-pro BNP levels with cardiac remodeling indices [44]. Sacubitril-valsartan-treated patients have shown a significant mean 9.4% increase in LVEF, and mean reductions in LVEDV -11.32 ml/m2, LVESV -14.15 ml/m2, left atrial volume index -7.06 ml/m2 and E/e' −0.93. These indices started to improve by 6 months but more pronounced at 1 year and underscore the potential benefit of reduction in NT-pro BNP levels and associated improvement in diastolic dysfunction.

Almufleh et al in year 2017 performed a single center, retrospective, cohort study on HFrEF patients (n=48) who were treated with Sacubitril/Valsartan for a median duration of 3 months (Interquartile range 2-6 months). Clinical and echocardiographic parameters were reviewed at three time points (pre-baseline which was median of 18 months before starting Sacubitril/Valsartan, baseline before treatment started, and post-Sacubitril/Valsartan). Sacubitril/Valsartan use was associated with an average 5% (±1.2) increase in EF, from a mean baseline of 25.33% to 30.14% (p<0.001) with a median duration of treatment 3 months. There was no significant change in mean LVEF over a median duration of 11 months (IQR 5.5-15.5) between pre-baseline and baseline time points prior to treatment (p=1.0). The mean increase in ejection fraction tended to be marginally greater in the medium/ high dose cohort as compared to the low dose cohort, with a mean increase of 5.09% (±1.36) and 4.03% (±3.17), respectively (p=0.184). There was a 3.36 mm reduction in left ventricular end-systolic diameter (p=0.04), a 2.64 mm reduction in left ventricular end-diastolic diameter (p=0.02), and a 14.4 g/m2 reduction in left ventricular mass index (p<0.01). It was concluded that

Sacubitril/Valsartan was found to improve EF and multiple measures of reverse remodeling beyond the effects of concomitant optimal medical therapy [45].

Bayard et al in year 2019 conducted a prospective study to see impact of sacubitril/valsartan on echo parameters in HFrEF patients. 52 HF patients were prospectively enrolled using PARADIGM-HF criteria: Class II, III, or IV HF; ejection fraction (EF) of 40% or less; hospitalized for HF within the previous 12 months. Echo was done at baseline and 3 months after optimal dose adjustment. Under sacubitril/valsartan, several echo parameters significantly improved: LVEF from 32.6 ± 5 to 36 ± 6% (p = 0.0001); LVES volume from 117 ± 40 to 108 ± 46 mL (p = 0.0051); SEV from 59 ± 12 to 64±13 (p=0.0061); LVEDD from 60±4 to 57±5mm (p=0.0002); mean right ventricular systolic pressure (RVSP) from39±10 to 32±8 (p=0.0001). No significant improvement occurred in LV diastolic parameters or RV echo parameters. So it was concluded that sacubitril/valsartan significantly improves LV systolic remodeling, without any significant effects on LV diastolic or RV systolic echo parameters [46].

Sacubitril-valsartan in functional mitral regurgitation

Secondary or functional mitral regurgitation (MR) is commonly seen in HFrEF patients and is a poor prognostic marker. Despite guideline-directed maximal medical treatment, 2-year mortality is of the patients admitted with HF is almost 50%. Interventional therapies to improve outcomes in this population include cardiac resynchronization therapy, LV assist devices, cardiac transplantation and transcatheter mitral valve repair. Although β-blockers, ACE inhibitors and ARBs could partially attenuate LV dilation and remodeling after myocardial injury, their effects on LV remodeling are insufficient for reducing the severity of MR.

The effect of sacubitril-valsartan on functional mitral regurgitation is noted in two studies. In their study Martens *et al.* have shown that volumetric remodeling was associated with a reduction in the degree of mitral

regurgitation (1.59 ±1.0 vs 1.11±0.8; p <.001; [scale from 0–4]) apart from the improvement in EF and other metrics mentioned above [43]. In PRIME trial (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation),Kang *et al.*, assessed the therapeutic impact of ARNI on functional MR by randomizing 118 patients with HF with chronic functional MR secondary to LV dysfunction to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for HF. Over 12 months follow-up, there was a significant 30% decrease in effective regurgitant orifice area and 33% decrease in regurgitant volume in the sacubitril/valsartan group compared with valsartan group (-0.058 } 0.095 vs -0.018 } 0.105 cm2; p = 0.032; mean difference, -7.3 ml; 95% CI: -12.6 to -1.9; p = 0.009) [47]. Though small in numbers, these studies again provide mechanistic explanation for the benefit of sacubitril-valsartan therapy in patients with HFrEF including functional MR.

ARNI & antiarrhthymic effect

De Diego *et al.* have reported the impact of sacubitril-valsartan treatment compared with ACEI/ARB in 120 patients with home monitored ICD over 18 months and found that sacubitril-valsartan reduced PVCs, non sustained ventricular tachycardia (VT), ventricular arrhythmias and appropriate shocks [48]. These findings may suggest an important role for sacubitril-valsartan in reduction of sudden cardiac death in patients with HFrEF. The possible mechanisms of this benefit may be related to the effect of sacubitril-valsartan on improvement in hemodynamic, improvement in LV function, reduction in myocardial fibrosis and reduction in sympathetic nervous system tone. It is not yet known whether sacubitril-valsartan has direct antiarrhthymic effects.

ARNI & glycemic control

In an interesting *post hoc* analysis of PARADIGM HF study, Seferovic *et al.* reported findings that patients receiving sacubitril-valsartan had a great glycemic control evidenced by HbA1C reduction compared with those on enalapril. The authors reported a total of 3778 (45%) patients were found

to be having diabetes and assessed their glycemic control by HbA1c measurements yearly up to 3 years. Patients in sacubitril-valsartan arm (n = 1904) had greater reduction in HbA1c levels, lesser need for initiation of new insulin therapy compared with those on enalapril (n = 1874) [49]. These findings could be explained by the neprilysin inhibition by sacubitril-valsartan. Neprilysin inhibition is associated with increase in bradykinin that causes increase in insulin sensitivity and an increase in GLP-1 that causes increased insulin release and decreased glucagon secretion.

ARNI & strain analysis

Biering-Sorensen in 2018 conducted a phase 2, randomized, parallel-group, double-blind multicenter trial in 301 patients with New York Heart Association (NYHA) class II-III HF, LVEF ≥45%, and NT-proBNP ≥400 pg/mL. Participants were randomly assigned (1:1) to sacubitril/ valsartan titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily for 36 weeks. Patients were assessed for change in GLS (global longitudinal strain) and GCS(global circumferential strain) from baseline to 36 weeks, adjusting for baseline value, in patients with sufficient imaging quality for 2D speckle tracking analysis at both time points (n=60 S/V, 75 valsartan only). GCS was significantly improved at 36 weeks in the SACUBITRIL/VALSARTAN group when compared with the valsartan group (Δ 4.42, p=0.021), with no significant difference observed in GLS (Δ0.25, p=0.73). It was concluded that in patients with HFpEF, S/V improved global circumferential but not longitudinal strain when compared to valsartan during a 36 weeks period [50].

ARNI and 6 MWT

Beltran et al conducted a study to see effects of Sacubitril/valsartan on 6-minute walk test in HFrEF patients. 58 stable symptomatic patients with HFrEF were eligible for sacubitril/valsartan and underwent 6-MWT before and 30 days after initiation of sacubitril/valsartan therapy. The mean (SD) values of baseline LVEF and 6MWT were 30±7%, and 300±89m, respectively. Compared with baseline, the 6-MWT distance increased

significantly at 30 days by 13.9% (+Δ = 41.8 m (33.4–50.2); p < 0.001). Thus it was concluded that sacubitril/valsartan was associated with an improvement in exercise tolerance in symptomatic patients with HFrEF [51].

MATERIALS AND METHODS

This was a hospital based study done in total of 100 patients from the period of May 2019 to June 2020 with the aim of assessment of CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN in OPD/IPD of Hero DMC Heart Institute, Ludhiana, Punjab.

The study population consisted of 100 patients with HFrEF who were already on ARBs (valsartan{60}/losartan{40}) in addition to optimal medical therapy in DMC & HOSPITAL. These patients were analyzed at baseline for NYHA FUNCTIONAL CLASS, 6 minute walk test and transthoracic echocardiography. Imaging data was analyzed for LV dimensions and volume.

These patients were followed up for 6 months and reassessed for NYHA FUNCTIONAL CLASS, 6 minute walk test and transthoracic echocardiography. Only 94 patients were assessed at 6 months as 6 patients died during follow up.

At 6 months these 94 patients were given option for SACUBITRIL/ VALSARTAN combination and 26 patients opted for SACUBITRIL/ VALSARTAN and switched over to SACUBITRIL/VALSARTAN while 68 patients continued on ARBs. All patients were followed up for additional six months and reassessed for NYHA class, 6 minute walk test and TTE at 1 year. During follow up 1 patient died in SACUBITRIL/VALSARTAN group and 25 patients completed the study whereas 1 patient died and 4 patients lost to follow up due to pandemic situation in ARB group and 63 patients completed the study.

At the end of 1 year comparison was made between patients who were switched over to SACUBITRIL/VALSARTAN versus patients who continued ARBs. Also comparison was made between the clinical parameters and echocardiographic features at 6 months versus at 1 year.

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina [16].

The six-minute walk test is a simple, inexpensive, and reproducible method for the assessment of exercise capacity. During the test, the patient walks the longest possible distance within the time of 6 minutes on the flat surface and can stop or slow down at any time and then resume walking during the test. The main result of the six-minute walk test (6MWT) is the distance covered by the patient in 6 minutes. The 6MWT shows good correlation with the peak VO2 from cardiopulmonary exercise test and is much easier to perform, and it reflects well the daily activities of the patients [17].

TTE was used for measurement of LV dimensions and volume. The most commonly used 2D method for volume measurements was the biplane method of discs (modified Simpson's rule) [18]. The principle underlying this method is that the total LV volume is calculated from the summation of a stack of elliptical disks. LV volumes measured from apical 4 and/or apical 2 chamber views, tracing the endocardial border of the LV. If there was no wall motion abnormality, the EF was estimated from one view only, apical 4 chambers or apical 2 chamber view. The ejection fraction was calculated from the difference between end-diastolic and end-systolic LV volume, divided by the end-diastolic LV volume.

SOURCE OF DATA

Data collection was done by analyzing the patients with HFrEF enrolled from DMC & HOSPITAL at baseline, 6 months and 1 year.

METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA: Patients with HFrEF (EF<40%).

EXCLUSION CRITERIA: 1.Symptomatic hypotension.

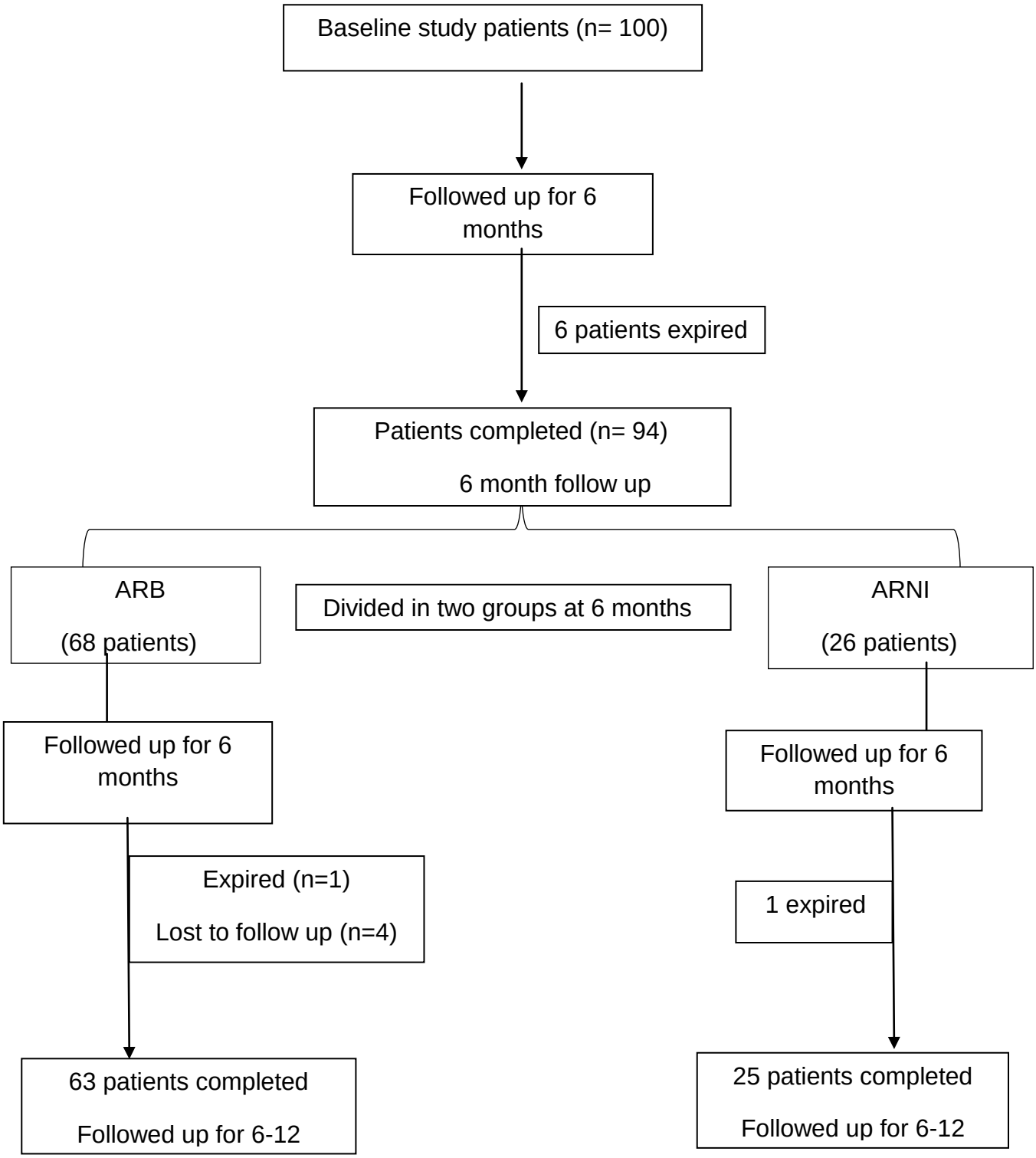
2. An estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area.

3. Serum potassium level of more than 5.5 mmol per liter.

4. History of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs.

STATISTICAL ANALYSIS: After data has been collected, it was subjected to analysis using appropriate statistical methods. The data obtained at various stages of the study was compared taking into account the specific objectives of the study.

STUDY FLOW CHART



OBSERVATION AND RESULTS

This was a hospital based study done in total of 100 patients from the period of May 2019 to June 2020 with the aim of assessment of clinical and echocardiographic features in HFrEF patients switched from ARBs to sacubitril/valsartan in OPD/IPD of Hero DMC Heart Institute, Ludhiana.

Table 1: Baseline characteristics of the patients

VARIABLE	**TOTAL POPULATION (100)**
Age(years) ± SD	61.67±10.47
Male (n, %)	65(65%)
ICMP (n, %)	44(44%)
NICMP (n, %)	56(56%)
T2DM (n, %)	38(38%)
HTN (n, %)	44(44%)
BASELINE BNP(pg/ml) ± SD	856.07 ±625.12
BASELINE Na+(mg/dl) ± SD	136.57±3.97
BASELINE K+(mg/dl) ± SD	4.30±0.40
BASELINE Creatinine (mg/dl) ± SD	0.95±0.30
NYHA II (n,%)	61(61%)
NYHA III (n, %)	19(19%)
NYHA IV (n, %)	20(20%)
BASELINE LVEF(%) + SD	30.12±6.28
Duration of Heart Failure(months)	25.5(11-44.5)

Table 1 shows the baseline characteristics of the patients enrolled in the study. The patients enrolled were above 32 years of age with a range including 33 to 86 years of age and a mean of 61.67 years. The male to female ratio in the study population was 1.85:1, with 65 males and 35 females. The patients with a history of ischemic cardiomyopathy constituted 44% of the study population, while 56% patients had dilated cardiomyopathy. The percent of diabetics were 38% and the hypertensive patients were 44% of the study population. The baseline BNP of the study population was 856.07 (pg/ml) (SD=625.12). The baseline Na+, K+, creatinine of the study population was 136.57 mg/dl (SD=3.97), 4.3 mg/dl (SD=0.40), 0.95 mg/dl (SD=0.30) respectively. At baseline 61% patients were in NYHA functional class II, 19% patients were in NYHA functional class III and 20% patients were in NYHA functional class IV. The baseline ejection fraction of the study population was 30.12 % (SD=6.28). The median (25^{th}-75^{th} percentile) duration of heart failure was 25.5 months (11-44.5 months).

Table 2: Distribution of the Age among total cases evaluated

AGE GROUP	No. of cases	Percentage
< 50	14	14.0%
51-60	35	35.0%
61-70	31	31.0%
> 70	20	20.0%
Total	100	100.0%

Table no. 2 and figure 1 shows the age range of patients. The minimum age being 33 years to maximum age 86 years with a mean age of 61.69 years. The maximum number of patients were in between 51-60 years of age (35%) while age group between 61-70 years of age had 31%., while 14 % patients had age below 50 years and 20% patients were age above 70 years of age.

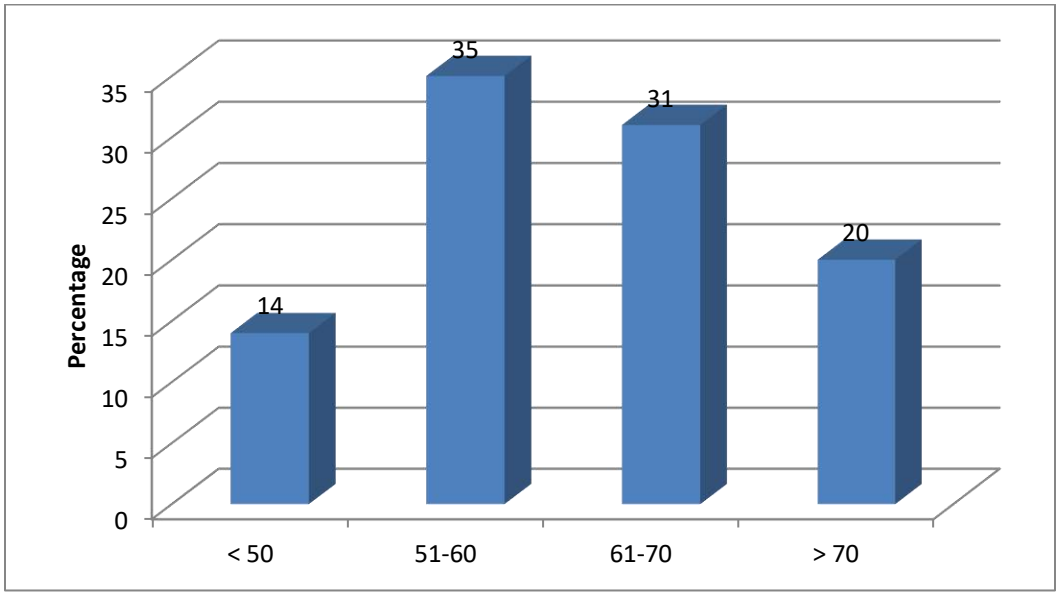


Figure 1: Distribution of patients in different age groups

Table 3: Gender distribution among total cases evaluated

SEX	No. of cases	Percentage
F	35	35.0%
M	65	65.0%
Total	100	100.0%

Table no.3 and figure 2 shows the sex wise distribution of the cases. Of the 100 patients enrolled, 65 (65%) were males and 35 (35%) were females.

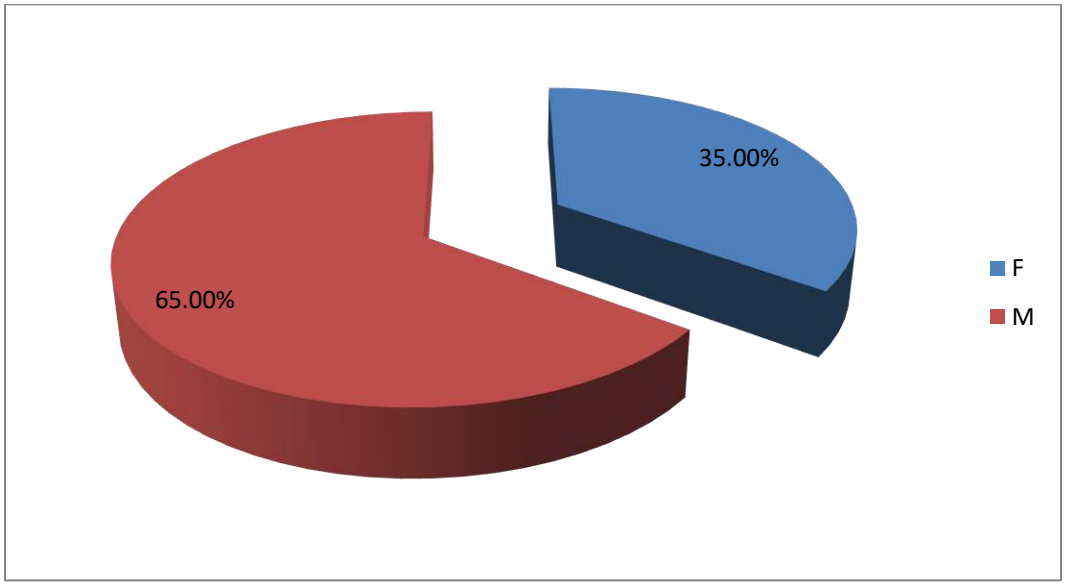


Figure 2: Gender distribution among total cases.

Table 4: Distribution of presenting complaints among the cases enrolled

COMPLAINTS	No. of cases	Percentage
CHEST PAIN	34	34.0%
DOE	84	84.0%
PAPITATION	13	13.0%
FATIGUE	3	3.0%
SYNCOPE	2	2.0%
Oedema	2	2.0%
No complaint	0	0.0%

Table 4 and figure no. 3 shows the distribution of the patients according to the presenting complaints at the time of enrollment in the study. Most common presenting complaint was Dyspnoea (84%) patients followed by chest pain (34%) patients.13% of the patients had palpitation, 3% patients had fatigue and 2% patients had syncope and edema each. Thus dyspnoea on exertion constituted the predominant complaint of the patients of enrolled in the study.

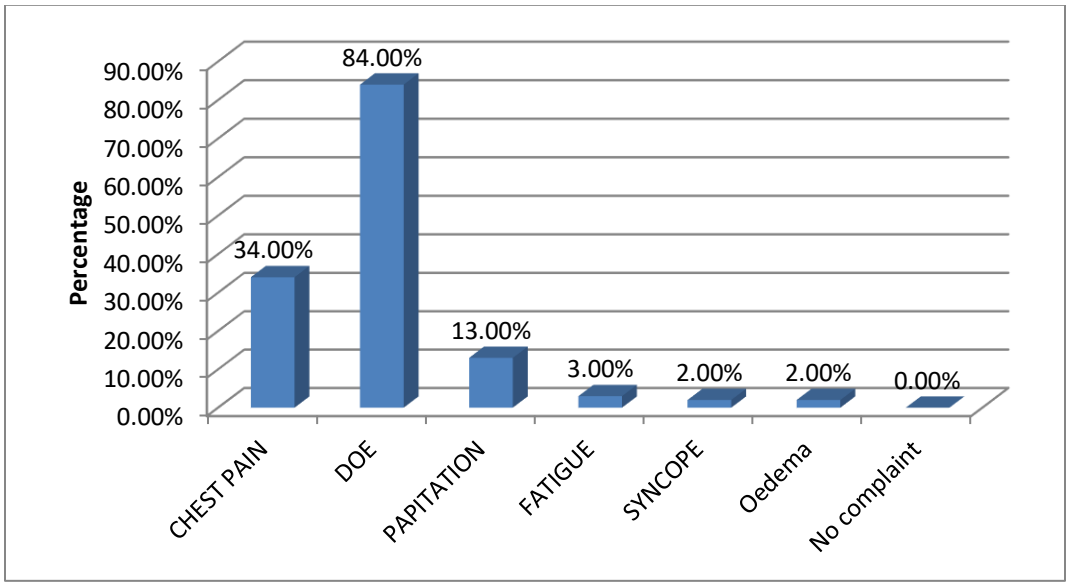


Figure 3: Distribution of associated complaints among the cases enrolled.

Table 5: Associated comorbidities among the patients enrolled

PAST HISTORY	No. of cases	Percentage
DM	38	38.0%
HTN	44	44.0%
COPD	3	3.0%
CVA	6	6.0%
HYPOTHYROIDISM	3	3.0%
AF	10	10.0%
CABG	5	5.0%

Table 5 and figure 4 shows the distribution of different co-morbidities that were observed in the enrolled patients. The majority of the cases had history of hypertension (44%) patients followed by diabetes mellitus (38%), atrial fibrillation (10%), CVA (6%), CABG (5%), hypothyroidism (5%) and COPD (3%).

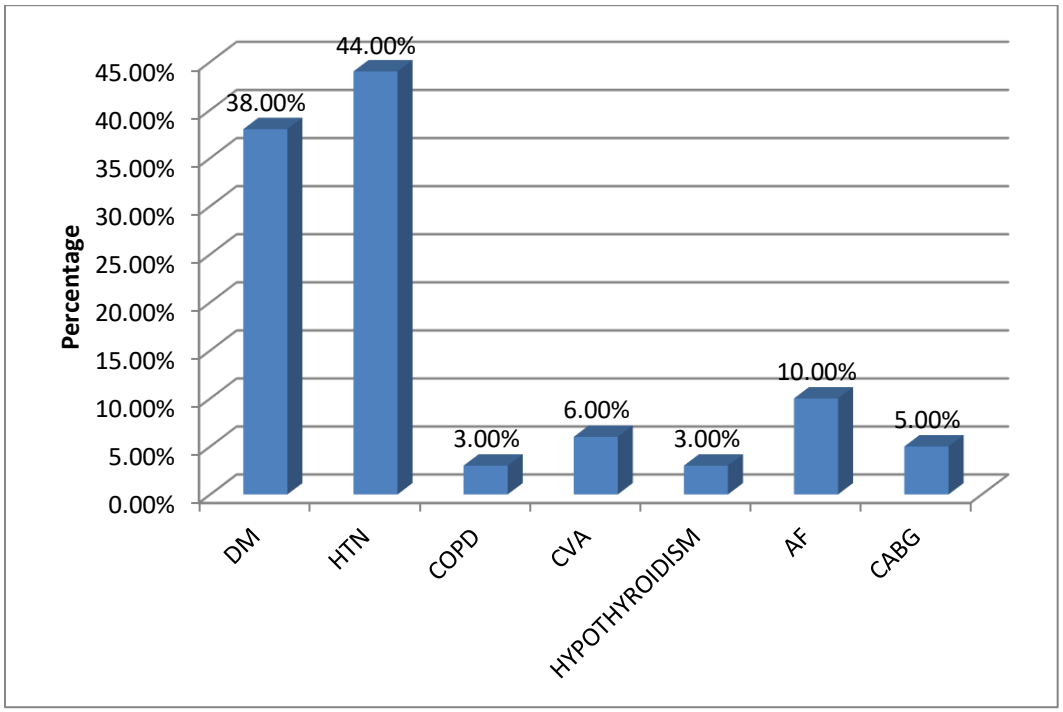


Figure 4.Distribution of various comorbidities among the patients enrolled.

Table 6: Distribution of baseline therapy among the cases enrolled.

Baseline THERAPY	No. of cases	Percentage
B Blockers	36	36.0%
IVABRADINE	10	10.0%
ARB	100	100.0%
MRA	63	63.0%
DIURETICS	89	89.0%
DIGOXIN	19	19.0%
CRT-D	1	1.0%
PPI	1	1.0%
ICD	2	2.0%

Table 6 and figure 5 shows distribution of baseline heart failure drugs prescribed among the cases enrolled. All patients were on Angiotensin receptor blockers. 89% patients were on diuretics while 63% were on mineralocorticoid receptor antagonists. Beta blockers were prescribed to 36% of patients, 19% patients was on digoxin, 10% patients were on Ivabradine and 2% patients had ICD and 1% had CRT-D and PPI each.

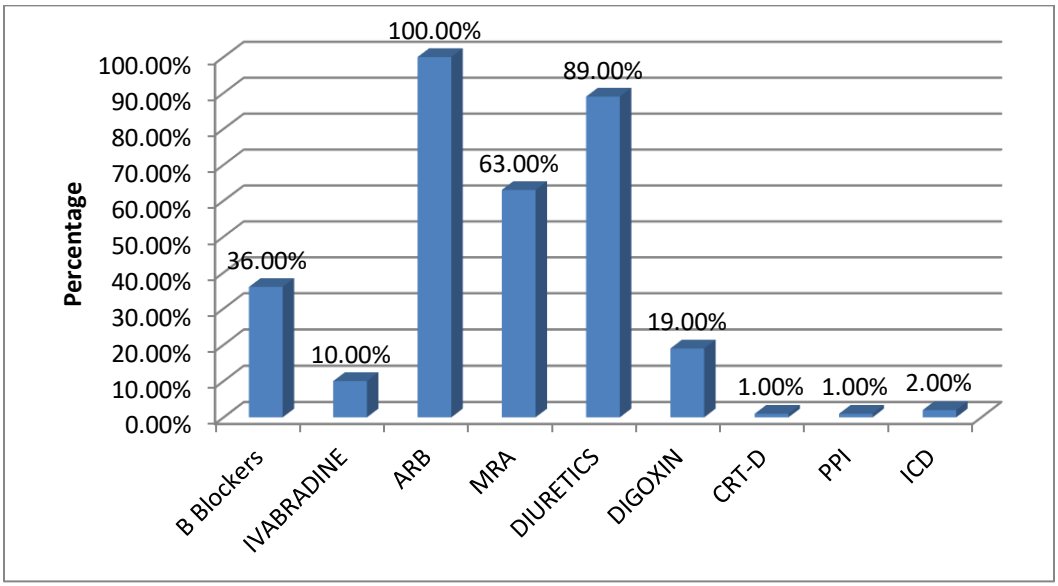


Figure 5: Distribution of drugs among the cases enrolled.

Table 7: Baseline ECG changes among the cases enrolled.

BASELINE ECG	No. of cases	Percentage
AF	10	10%
NSR/Intermittent AF	2	2%
AF/LBBB	1	1.0%
NSR	63	63.0%
NSR/BIFASCICULAR BLOCK	1	1.0%
NSR/IVCD	5	5.0%
NSR/LAFB	3	3.0%
NSR/LBBB	12	12.0%
NSR/RBBB	1	1.0%
PACED	2	2.0%
Total	100	100.0%

TABLE 7 and figure 6 shows baseline ECG changes among the patients enrolled.87% patients had Normal sinus rhythm at baseline while 11% patients had AF and 2% patients had paced rhythm. 13% patients had LBBB, 5% patients had nonspecific intraventricular conduction defect, 3% had LAFB, 1% had RBBB and bifascicular block each.

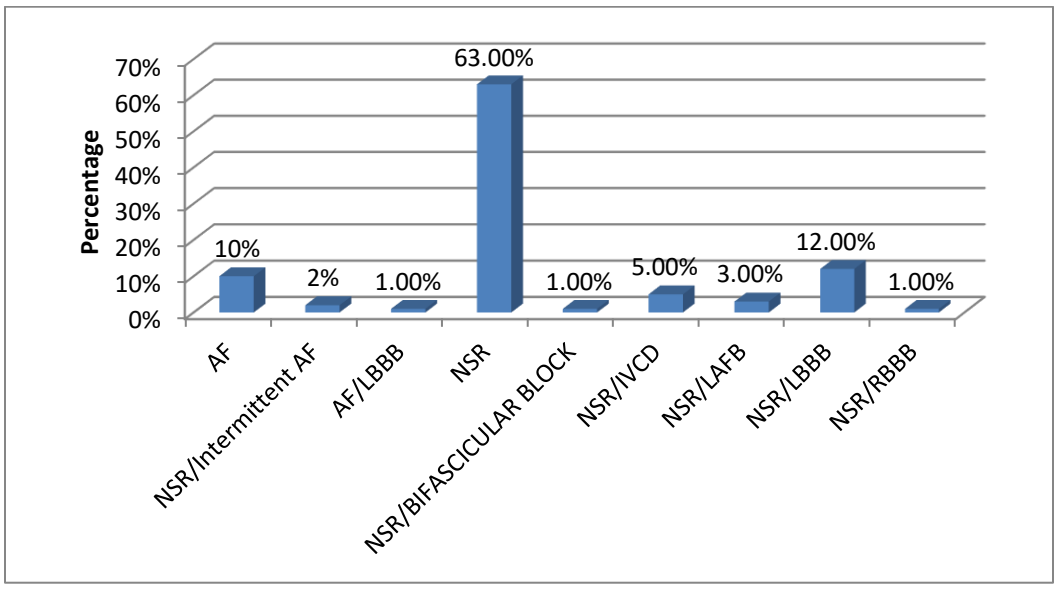


Figure 6: Baseline ECG changes among the cases enrolled.

Table 8: Baseline clinical and echocardiographic parameters among cases enrolled

Variable	N	Minimum	Maximum	Mean	Std. Deviation
6MWD (m)	99	60.00	420.00	282.98	75.79
EF (%)	100	18.00	42.00	30.12	6.28
LVIDs (mm)	100	30.00	68.00	49.42	8.15
LVIDd (mm)	100	42.00	78.00	61.59	9.16
LA diameter(mm)	100	28.00	65.00	43.38	8.17
MV E/A	89	0.30	2.40	1.14	0.40
PASP (mmHg)	100	20.00	90.00	37.78	14.85
TAPSE(mm)	100	10.00	28.00	20.78	4.32

Table 8 shows baseline clinical and echocardiographic parameters among cases enrolled. 99 patients had 6 min walk distance test done, maximum distance walked was 420 m and minimum distance was 60 m with mean of 282.98 m. Baseline EF in 100 patients had mean of 30.12%, maximum was 42% and minimum was 18%. LVIDs baseline had mean of 49.42 mm, the maximum was 68mm while minimum was 30 mm. LVIDd baseline had mean of 61.59 mm, maximum was 78 mm and minimum was 42 mm. Baseline LA diameter in 100 patients had mean of 43.48 mm, maximum was 65 mm and minimum was 28 mm. Baseline MV E/A in patients had mean of 1.14 with maximum of 2.40 and minimum of 0.30 in 89 patients as 11 patients had AF at baseline. Baseline maximum PA pressures were 90 mmHg and minimum pressures were 20 mmHg with mean of 37.38 mmHg. Baseline maximum TAPSE was 28 mm and minimum TAPSE was 10 mm with mean of 20.78 mm.

Table 9: Baseline MR Severity among cases enrolled

MR SEVERITY BASELINE	No. of cases	Percentage
Mild	32	32.0%
Mod	25	25.0%
NO	31	31.0%
Sev	11	11.0%
Total	100	100.0%

Table 9 and figure 7 shows baseline MR severity among cases enrolled in the study. Mild MR was seen in 32% patients, moderate MR in 25% patients, severe MR in 11 % patients while no MR was seen in 31 % patients.

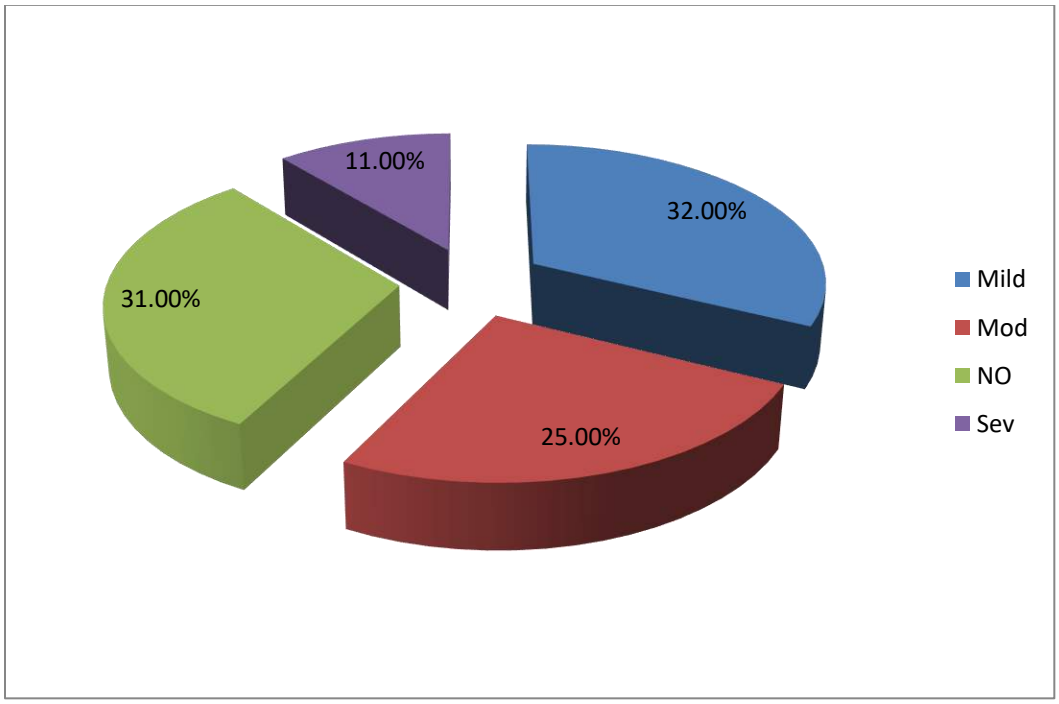


Figure 7: Baseline MR Severity among cases enrolled

Table 10: Comparison of baseline and 6 month clinical and echocardiographic parameters among cases enrolled.

	Baseline		6 month		t	p-value	Difference	
	Mean	SD	Mean	SD			Mean	SD
6 MWD	288.39	74.03	298.18	61.61	-1.638	0.105	-9.79	57.92
EF (%)	30.10	6.23	31.21	7.56	-1.694	0.094	-1.12	6.39
LVIDs	49.70	7.90	48.45	9.48	1.448	0.151	1.26	8.40
LVIDd	61.98	8.92	61.34	11.17	0.854	0.395	0.64	7.25
LA	43.54	8.29	44.32	8.45	-1.239	0.218	-0.78	6.08
MV E/A	1.14	0.41	1.18	0.46	-1.736	0.086	-0.04	0.20
PASP	37.67	14.86	37.48	12.00	0.135	0.893	0.19	13.78
TAPSE	20.51	3.87	19.79	3.91	1.381	0.059	0.72	2.95

At 6 months, clinical and LV remodelling parameters were taken and comparison between baseline and 6 month parameters was done. 6 min walk distance at baseline and at 6 months was 288.39m and 298.18m respectively and there was insignificant improvement with p value of 0.105. Ejection fraction mean value at baseline was 30.10% and at 6 months was 31.21% and there was insignificant improvement (p value 0.094). Similarly, there was no significant improvement between other LV remodeling parameter like LVIDs, LVIDd, LA diameter, MV E/A, PASP and TAPSE between baseline and 6 months (all *p* values >.05).

Figure 8: Baseline and 6 month clinical and echocardiographic parameters among cases enrolled.

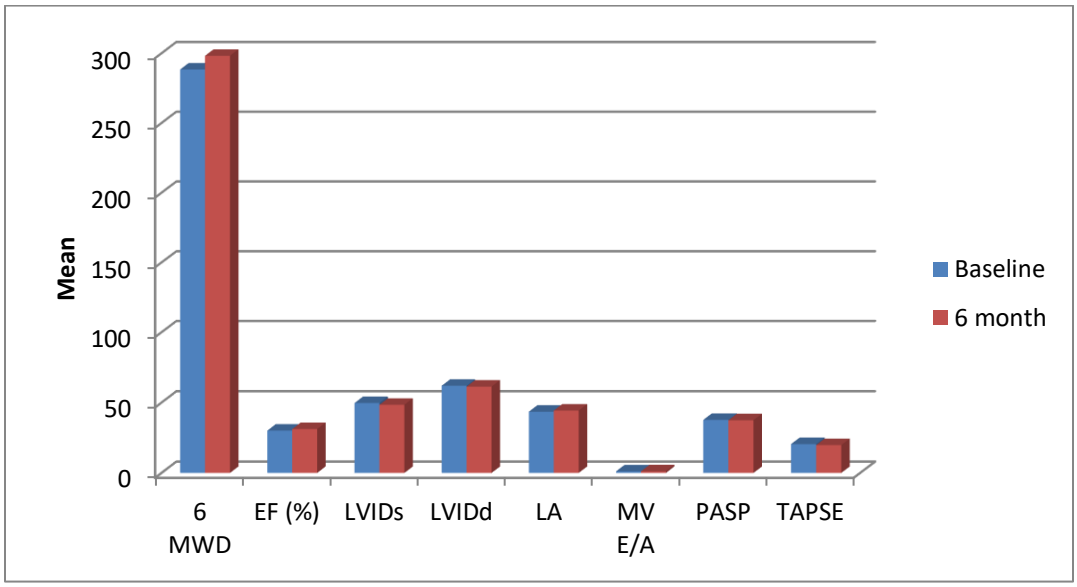


Table 11: Comparison of NYHA functional class at baseline and at 6 months among cases enrolled.

NYHA CLASS	Baseline		6 MONTHS		McNemar-Bowker Test	p-value
	No. of cases	Percentage	No. of cases	Percentage		
II	61	61.0%	55	58.5%	13.667	0.001
III	19	19.0%	34	36.2%		
IV	20	20.0%	5	5.3%		
Total	100	100.0%	94	100.0%		

Table 11 and figure 9 shows comparison of NYHA functional class at baseline and at 6 months among patients. There was significant improvement in NYHA functional class at 6 months as compared to baseline with p value of 0.001.

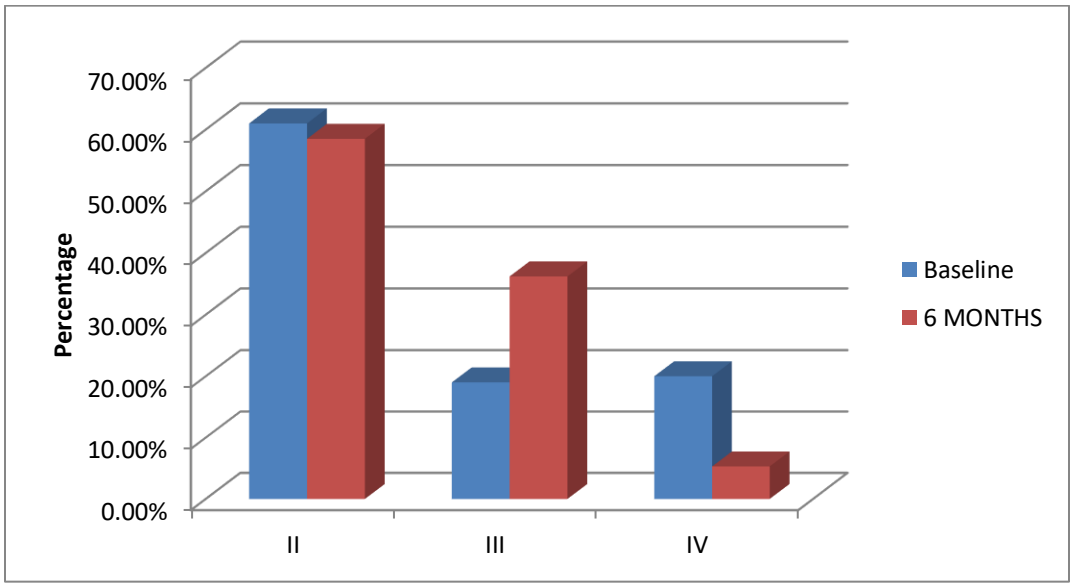


Figure 9: NYHA functional class at baseline and at 6 months among cases enrolled.

Table 12: Comparison of baseline and 6 month MR severity among cases enrolled.

MR Severity	Baseline		6 Months		McNemar-Bowker Test	p-value
	No. of cases	Percentage	No. of cases	Percentage		
Mild	32	32.0%	30	31.9%	8.889	0.18
Moderate	25	25.0%	27	28.7%		
NO	31	31.0%	28	29.8%		
Severe	11	11.0%	9	9.6%		
Total	100	100.0%	94	100.0%		

Table 12 and figure 10 shows MR severity at baseline and at 6 months among cases enrolled in the study. At baseline and at 6 months, MR severity was compared. Mild MR was seen in 32% at baseline vs 31.9% at 6 months ,moderate MR was seen in 25% at baseline vs 28.7% at 6 months ,severe MR in 11% vs 9.6% at 6 months and no MR seen in 31%vs 29.8% at 6 months. There was no significant difference in MR severity (p value 0.18).

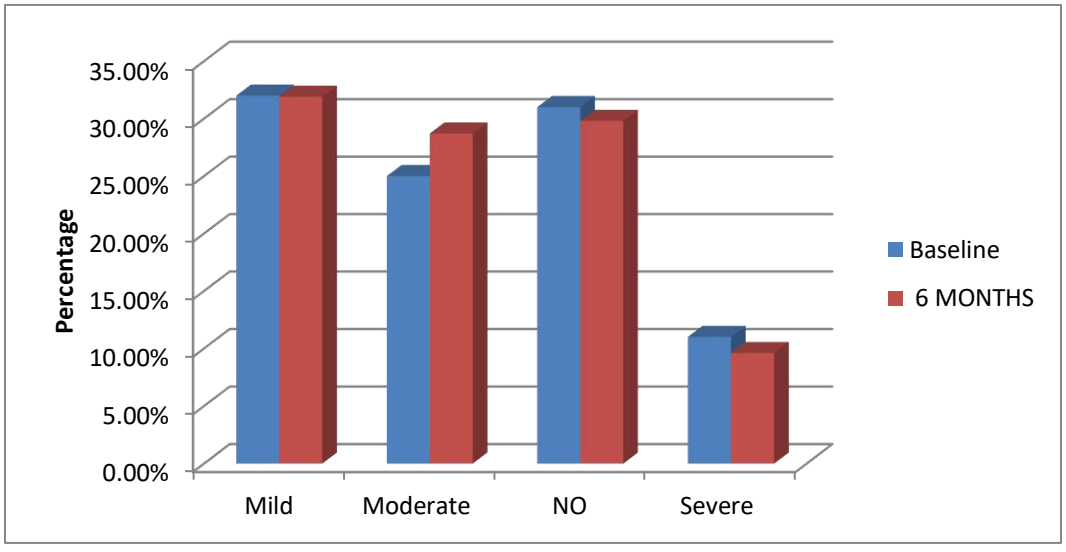


Figure 10: **Baseline and 6 month MR severity among cases enrolled.**

Table 13: Comparison of mean age between ARB and ARNI group

	ARB		ARNI		t	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
AGE	62.00	9.71	60.81	12.54	0.498	0.620	-3.56	5.95

At 6 months patients were divided into two groups ARB and ARNI. Table 13 and figure 11 shows comparison of mean age between ARB and ARNI group. There was no significant difference of mean age between ARB group (62 years) and ARNI group (60.81years) with p value of 0.620.

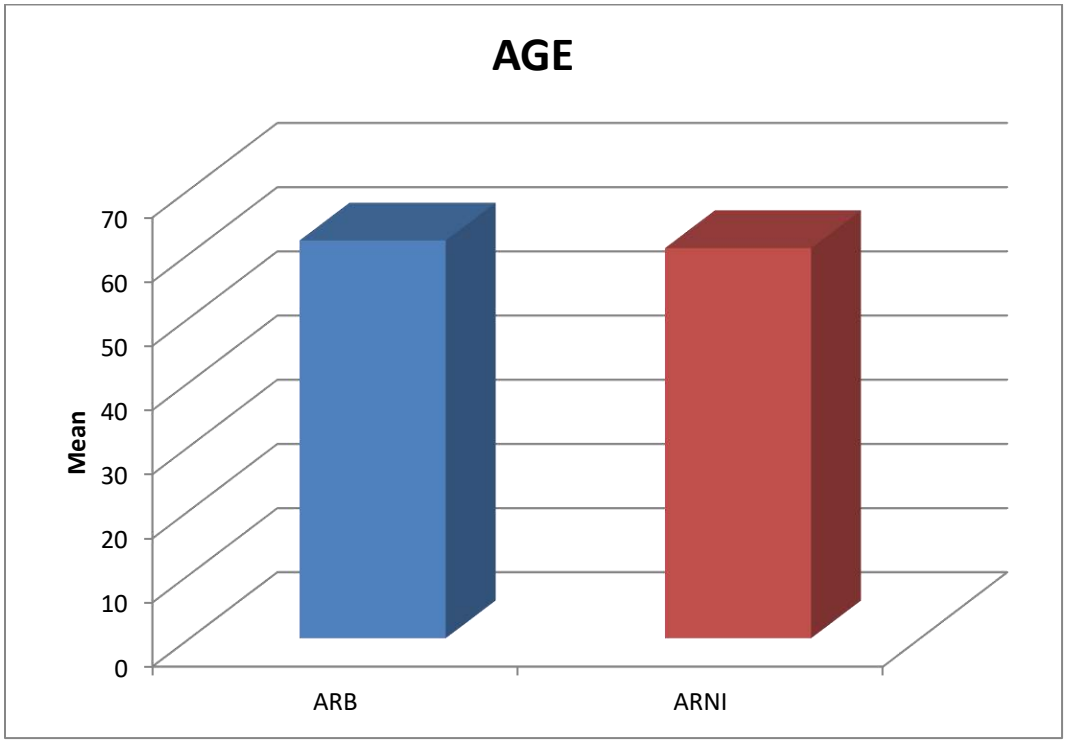


Figure 11: Comparison of mean age between ARB and ARNI group

Table 14: Comparison of different age groups between ARB and ARNI group.

		Group				Total	Chi square value	p value
		ARB		ARNI				
AGE GROUP	< 50	8	10.80%	9	34.60%	17	9.232	0.026
	51-60	26	35.10%	9	34.60%	35		
	61-70	27	36.50%	4	15.40%	31		
	> 70	13	17.60%	4	15.40%	17		

Table 14 and figure 12 shows comparison of different age groups between ARB and ARNI group. There was no significant difference (p value 0.026) between different age groups.

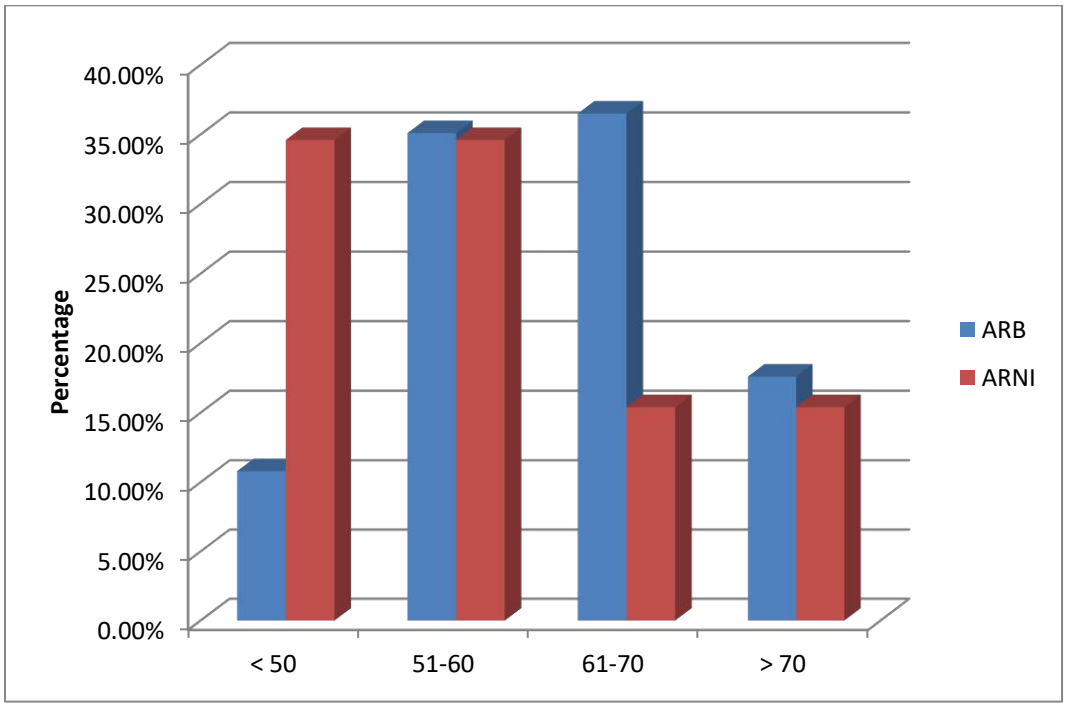


Figure 12: Comparison of different age groups between ARB and ARNI group.

Table 15: Comparison of male to female ratio in both groups.

		Group				Total	Chi square value	p value
		ARB		ARNI				
SEX	F	27	36.50%	8	30.80%	35	0.276	0.599
	M	47	63.50%	18	69.20%	65		

Table 15 and figure 13 shows comparison of male to female ratio between ARB and ARNI group. In comparison to ARB vs ARNI group, female were 27 vs 8 while male were 47 vs 18. No significant difference between two groups (p value 0.599).

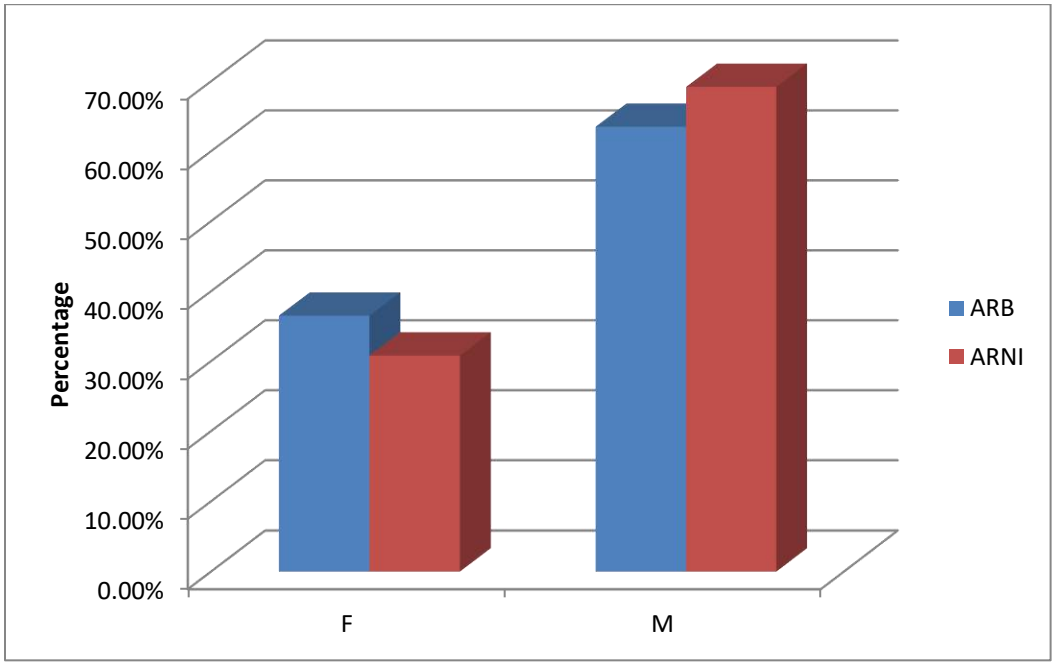


Figure 13: Comparison of male to female ratio in both groups.

Table 16: Comparison of heart failure etiology between both groups.

		Group				Total	Chi square value	p value
		ARB		ARNI				
ETIOLOGY OF HF	ICMP	34	45.90%	10	38.50%	44	0.437	0.508
	NICMP	40	54.10%	16	61.50%	56		

Table 16 and figure 14 shows comparison of etiology of heart failure between ARB and ARNI group. In comparison between ARB vs ARNI group, patients with ischaemic cardiomyopathy (ICMP) were 45.90% vs 38.50% while non ischaemic cardiomyopathy patients were 54.10% vs 61.50% with no significant difference in etiology between both groups (p value 0f 0.508).

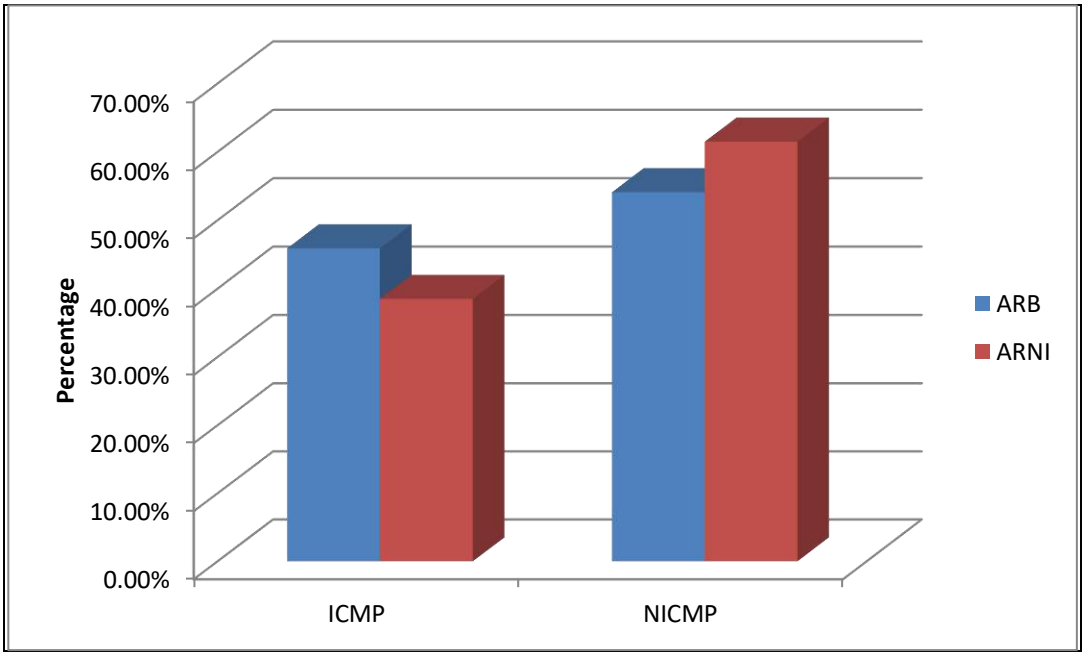


Figure 14: Comparison of heart failure etiology between both groups.

Table 17: Comparison of 6 MWD between ARB and ARNI group.

	ARB		ARNI		T	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
6 MWD 6 MONTHS	294.44	64.98	307.96	51.64	-0.951	0.344	-41.75	14.71
6 MWD 1 YEAR	291.21	60.67	396	30.71	-8.208	<.001	-124.30	-85.28
6 MWD 6-12 diff	-0.19	20.59	-87.32	36.96	14.065	<.001	70.81	99.44

Table 17 and figure 15 shows comparison of 6MWD between ARB and ARNI group. 6 MWD at 6 months in ARB group was 294.44 meters as compared to 307.96 meters in ARNI group with p value 0.34. 6 MWD at 12 months in ARB group was 291.21 meters vs 396 meters in ARNI group with p value less than 0.001. 6 min walk distance (6-12 month) difference in ARB group was -0.19 meters as compared to -87.32 meters in ARNI group with p value less than 0.001. Thus 6 min walk distance at 6 months had no significant difference between both groups while difference was significant at one year (p value < 0.001) and comparison of 6MWD (6-12month) difference in both groups was also significant (p <0.001).

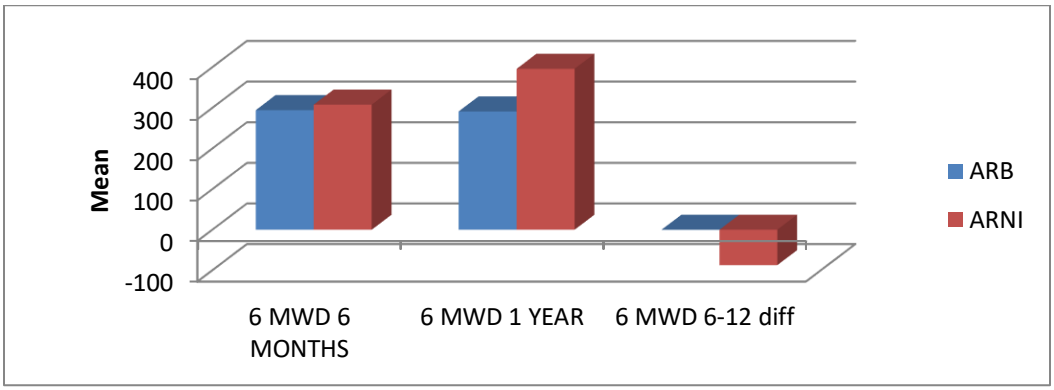


Figure 15: Comparison of 6 MWD between ARB and ARNI group.

Table 18: comparison of ejection fraction between ARB group and ARNI group.

	ARB		ARNI		t	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
EF 6 MONTHS	31.93	7.98	29.35	6.05	1.491	0.139	-0.86	6.02
EF 1 YEAR	31.95	8.90	33.88	7.73	-0.950	0.345	-5.96	2.11
EF 6-12 diff	-0.38	5.31	-4.64	5.54	3.352	0.001	1.73	6.78

Table 18 and figure 16 shows comparison of EF between ARB and ARNI group. There is no significant difference between ejection fraction at 6 months and at 12 months between both groups. Comparison of EF (6 -12 month) difference between both groups was significant with p value 0.001. Thus there was significant improvement in EF at 12 months in ARNI group.

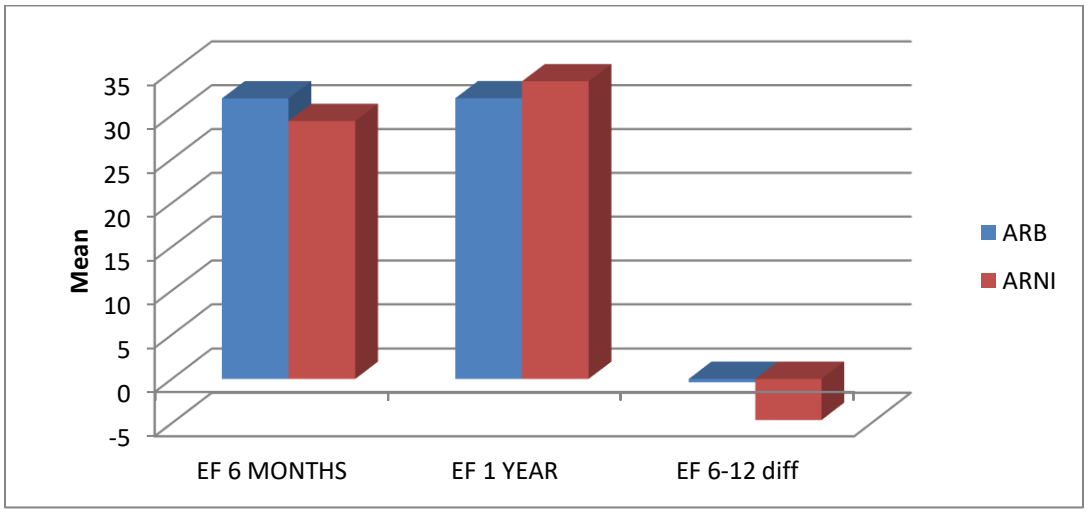


Figure 16: comparison of ejection fraction between ARB group and ARNI group.

Table 19: comparison of LV dimensions between ARB group and ARNI group.

	ARB		ARNI		t	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
LVIDs 6 MONTHS	48.41	9.49	48.54	9.64	-0.058	0.954	-4.49	4.24
LVIDs 1 YEAR	48.08	9.04	45.40	9.48	1.237	0.220	-1.63	6.99
LVIDs 6-12 diff	0.44	3.29	2.92	2.89	-3.294	0.001	-3.97	-0.98
LVIDd6 MONTHS	61.25	11.37	61.58	10.83	-0.126	0.900	-5.47	4.82
LVIDd1 YEAR	60.89	10.87	58.64	10.11	0.892	0.375	-2.76	7.26
LVIDd 6-12 diff	0.65	3.25	2.80	6.94	-1.981	0.050	-4.31	0.01

Table 19; figure 17 and 18 shows comparison of LV Dimensions between ARB and ARNI group. There was no significant difference between LV systolic dimension at 6 and 12 months between two groups while Comparison of difference in LVIDs at 6 and 12 months between both groups was significant with p value 0.001. Thus there was significant improvement in LVIDs at 12 months in ARNI group.

Similarly there was no significant difference between LV diastolic dimension at 6 and12 months between both groups and comparison of 6-12 month difference was significant with significant improvement in LVIDd at 12 months in ARNI group.

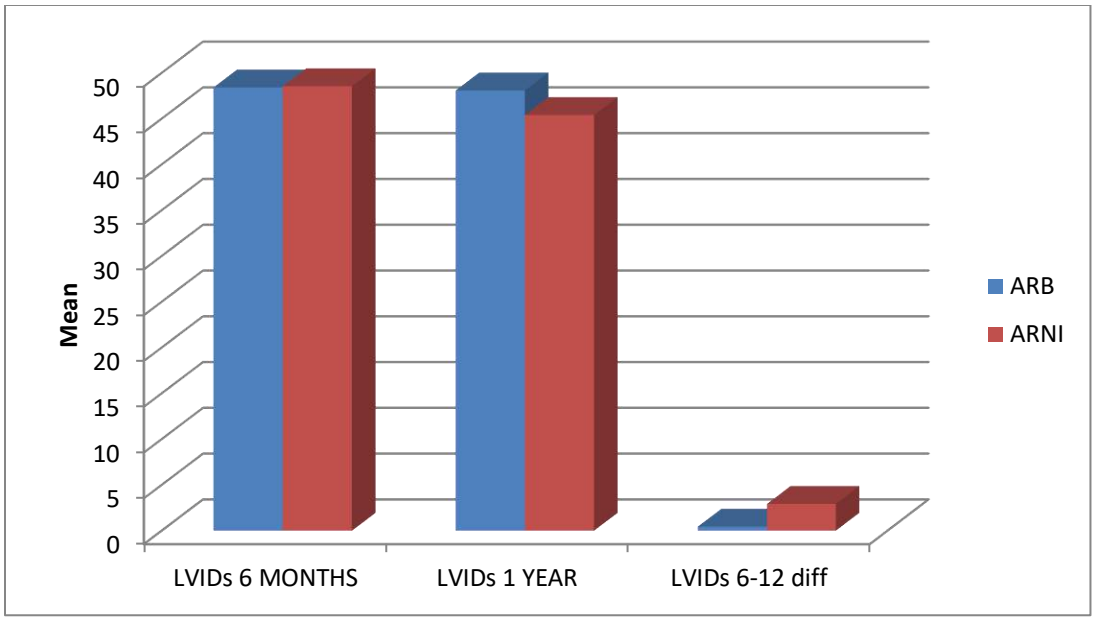


Figure 17: comparison of LVIDs between ARB group and ARNI group.

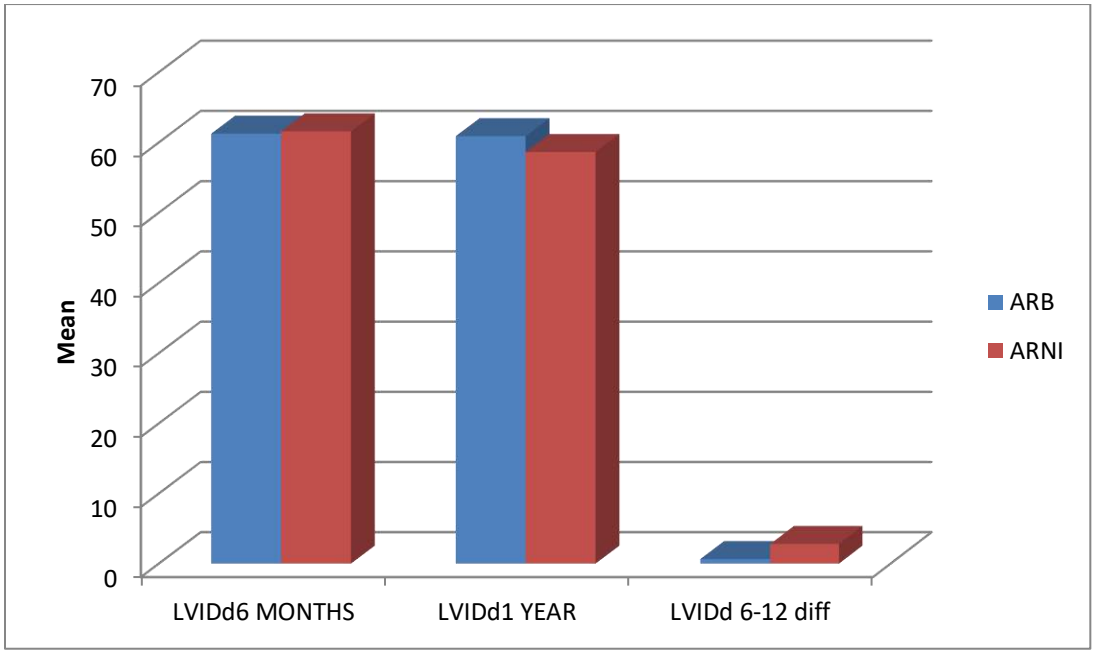


Figure 18: comparison of LVIDd between ARB group and ARNI group.

Table 20: Comparison of Left atrium diameter between ARB group and ARNI group.

	ARB		ARNI		t	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
LA 6 MONTHS	44.75	8.16	43.19	9.24	0.798	0.427	-2.32	5.43
LA 1 YEAR	44.94	8.02	39.79	8.91	2.593	0.011	1.20	9.09
LA 6-12 diff	-0.27	3.47	4.80	9.83	-3.592	0.001	-7.88	-2.26

Table 20 and figure 19 shows comparison of LA diameter between ARB and ARNI group. There was no significant difference between LA diameter at 6 months between two groups with insignificant p value while difference was significant at one year (p value 0.011) and comparison of LA diameter (6-12 month) difference between both groups was also significant (p <0.001).Thus there was significant improvement in LA diameter at 12 months in ARNI group.

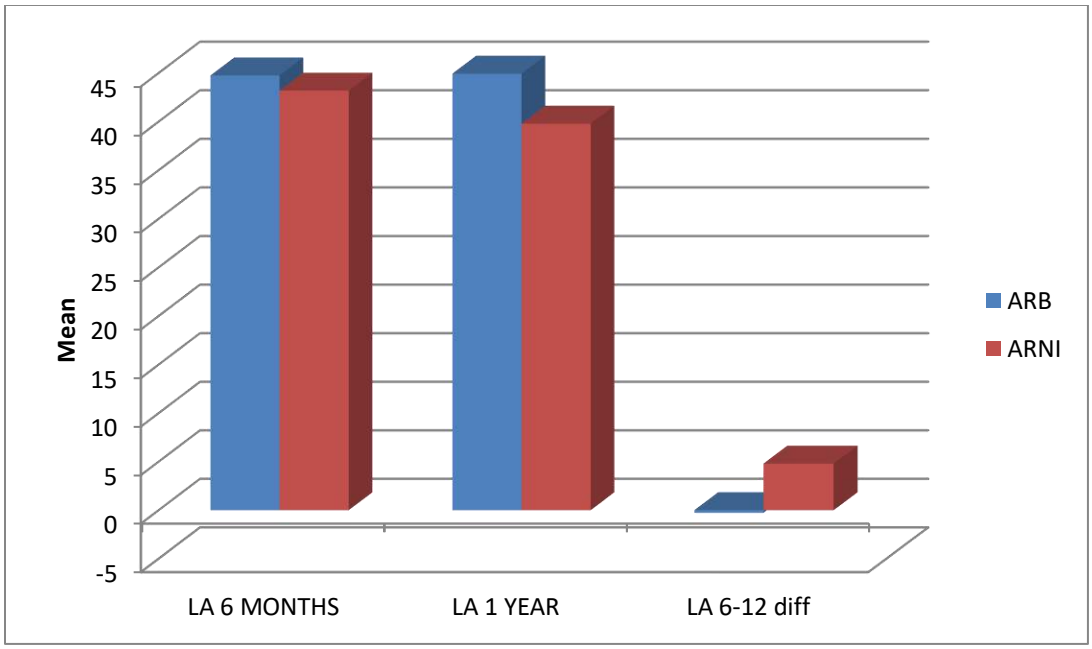


Figure 19: Comparison of Left atrium diameter between ARB group and ARNI group

Table 21: Comparison of Diastolic function between both groups.

	ARB		ARNI				95% CI of the Difference	
	Mean	SD	Mean	SD	t	p-value	Lower	Upper
MV E/A_6 MONTHS	1.22	0.46	1.09	0.46	1.15	0.254	-0.09	0.35
MV E/A_1 YEAR	1.22	0.38	1.07	0.37	1.605	0.113	-0.04	0.34
MV E/A_6-12 diff	-0.01	0.21	0	0.34	-0.018	0.986	-0.13	0.12

Table 21and figure 20 shows comparison of diastolic function between ARB and ARNI group. There was no significant difference in E/A ratio at 6 and 12 months and comparison of E/A ratio(6 - 12 month) difference between both groups was also insignificant with p value 0.986. Thus there was no improvement in diastolic function in both groups.

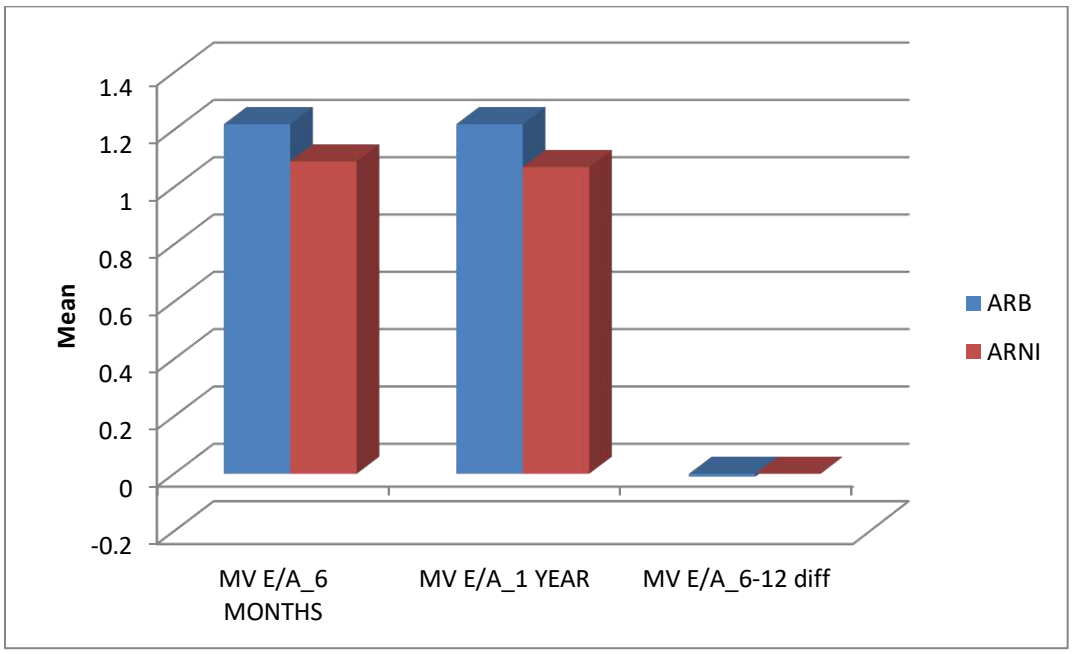


Figure 20: Comparison of Diastolic function between both groups.

Table 22: Comparison of pulmonary artery pressures between both groups.

	ARB		ARNI		t	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
PASP_6 MONTHS	37.50	12.26	37.42	11.54	0.028	0.978	-5.45	5.60
PASP_1 YEAR	37.84	10.07	32.80	8.50	2.209	0.030	0.50	9.58
PASP_6-12 DIFF	-0.06	8.84	4.12	9.02	-1.991	0.050	-8.36	-0.01

Table 22 and figure 21 shows comparison of pulmonary artery pressures between ARB and ARNI group. There was no significant difference in PASP at 6 months between both groups while difference was significant at one year (p value 0.030) and comparison of PASP (6-12 months) difference between both groups was also significant (p 0.050). Thus there was significant improvement in PASP in ARNI group patients.

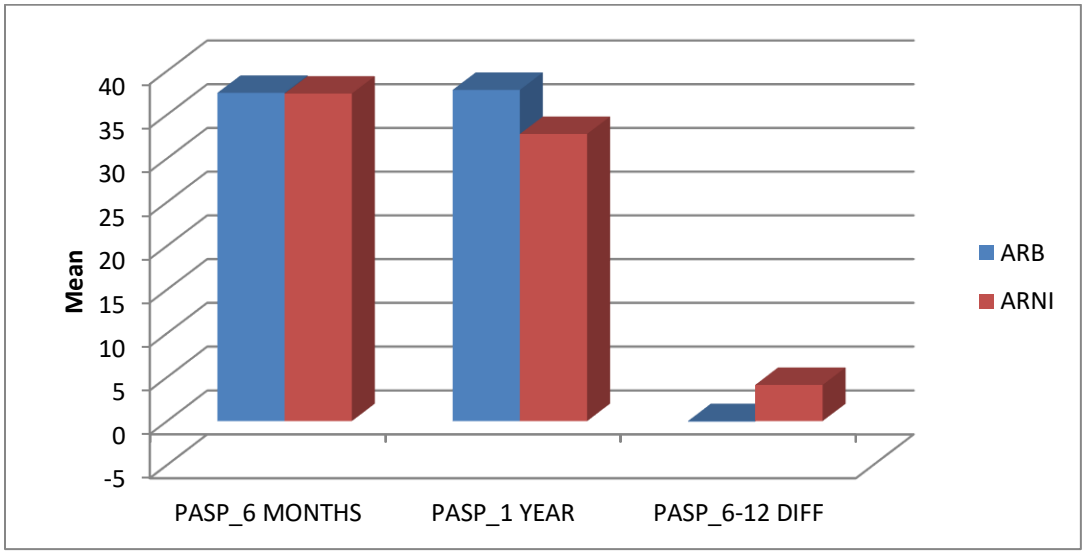


Figure 21: Comparison of pulmonary artery pressures between both groups.

Table 23: Comparison of Right ventricular function parameters between both groups.

	ARB		ARNI		t	p-value	95% CI of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
TAPSE 6 MONTHS	20.07	3.16	19.04	5.42	1.149	0.253	-0.75	2.82
TAPSE 1 YEAR	19.71	3.52	21.72	3.25	-2.462	0.016	-3.63	-0.39
TAPSE 6-12 DIFF	0.24	1.97	-2.68	4.18	4.46	<.001	1.62	4.22

Table 23 and figure 22 shows comparison of tricuspid annular plane systolic excursion between ARB and ARNI group. There was no significant difference in TAPSE at 6 months between both groups while difference was significant at one year (p value 0.016) and comparison of TAPSE (6 -12 months) difference between both groups was also significant (p <.001). Thus there was significant improvement in TAPSE in ARNI group patients.

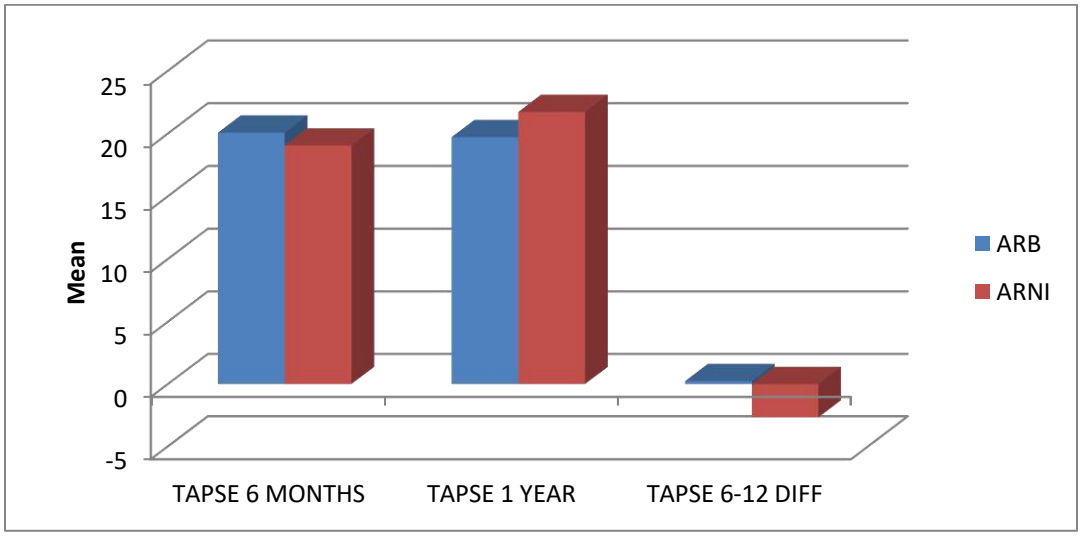


Figure 22: Comparison of Right ventricular function parameters between both groups.

Table 24: Comparison of NYHA functional class between both groups.

		Group 1				Total	Chi-square value	p-value
		ARB		ARNI				
NYHA CLASS_6 MONTHS	II	38	55.9%	17	65.4%	55	2.226	0.329
	III	25	36.8%	9	34.6%	34		
	IV	5	7.4%	0	0.0%	5		
NYHA CLASS_1 YEAR	II	29	46.0%	22	88.0%	51	12.896	0.002
	III	26	41.3%	3	12.0%	29		
	IV	8	12.7%	0	0.0%	8		

Table no 24 shows comparison of NYHA functional class between ARB and ARNI group. There was no significant difference of NYHA functional class at 6 months with p value 2.226, while there was significant improvement in NYHA functional class in ARNI group patients at 12 months with p value 0.002.

Table 25: Comparison of MR severity between both groups.

		Group 1				Total	Chi-square value	p-value
		ARB		ARNI				
MR SEVERITY_6 MONTHS	mild	20	29.4%	8	30.8%	30	0.056	0.996
	mod	27	39.7%	10	38.5%	27		
	no	15	22.1%	6	23.1%	28		
	sev	6	8.8%	2	7.7%	9		
MR SEVERITY_1 YEAR	mild	14	22.2%	7	28.0%	21	15.539	0.001
	mod	27	42.9%	3	12.0%	30		
	NO	12	19.0%	14	56.0%	26		
	sev	10	15.9%	1	4.0%	11		

Table no 25 shows comparison of MR severity between ARB and ARNI group. There was no significant difference of MR severity at 6 months with p value 0.996 while significant difference at 12 months with p value 0.001 between ARB and ARNI groups. Thus there was improvement in MR severity in patients on ARNI.

Table 26: Comparison of comorbidities between both groups.

PAST HISTORY		Group				Total	Chi-square value	p-value
		ARB		ARNI				
DM	N	44	59.50%	18	69.20%	62	0.78	0.377
	Y	30	40.50%	8	30.80%	38		
HTN	N	41	55.40%	15	57.70%	56	0.041	0.84
	Y	33	44.60%	11	42.30%	44		
COPD	N	71	95.90%	26	100.00%	97	1.087	0.297
	Y	3	4.10%	0	0.00%	3		
CVA	N	68	91.90%	26	100.00%	94	2.243	0.134
	Y	6	8.10%	0	0.00%	6		
HYPOTHYROIDISM	N	71	95.90%	26	100.00%	97	1.087	0.297
	Y	3	4.10%	0	0.00%	3		
AF	N	68	91.90%	22	84.60%	90	1.132	0.287
	Y	6	8.10%	4	15.40%	10		
CABG	N	71	95.90%	24	92.30%	95	0.536	0.464
	Y	3	4.10%	2	7.70%	5		

Table 26 and figure 23 shows comparison of comorbities between ARB and ARNI group. There was no significant difference in past history of DM, HTN, COPD, CVA, HYPOTHYROIDISM, AF and CABG between ARB and ARNI group patients.

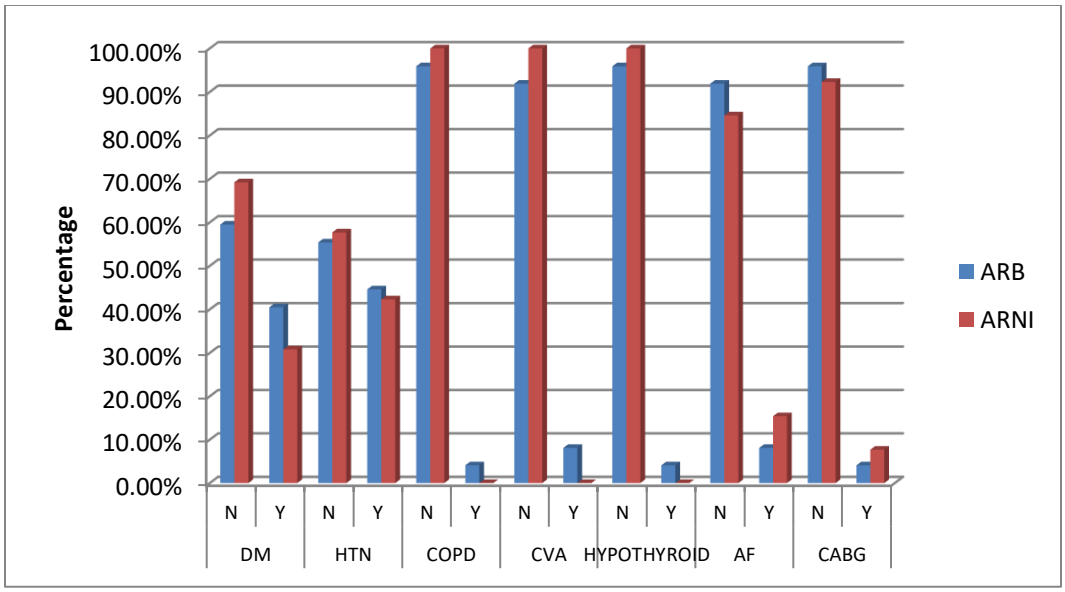


Figure 23: Comparison of comorbidities between both groups.

Table 27: Comparison of baseline medication between both groups.

Baseline THERAPY		Group				Total	Chi-square value	p-value
		ARB		ARNI				
B Blockers	N	50	67.60%	14	53.80%	64	1.572	0.21
	Y	24	32.40%	12	46.20%	36		
IVABRADINE	N	68	91.90%	22	84.60%	90	1.132	0.287
	Y	6	8.10%	4	15.40%	10		
MRA	N	31	41.90%	6	23.10%	37	2.922	0.087
	Y	43	58.10%	20	76.90%	63		
DIURETICS	N	7	9.50%	4	15.40%	11	0.69	0.406
	Y	67	90.50%	22	84.60%	89		
DIGOXIN	N	59	79.70%	22	84.60%	81	0.298	0.585
	Y	15	20.30%	4	15.40%	19		
CRT-D	N	73	98.60%	26	100.00%	99	0.355	0.551
	Y	1	1.40%	0	0.00%	1		
PPI	N	73	98.60%	26	100.00%	99	0.355	0.551
	Y	1	1.40%	0	0.00%	1		
ICD	N	73	98.60%	25	96.20%	98	0.611	0.434
	Y	1	1.40%	1	3.80%	2		

Table 27 and figure 24 shows comparison of baseline medications between ARB and ARNI group. There was no significant difference in both groups regarding use of b blockers, MRA, diuretics, digoxin, ivabradine and PPI/CRT.

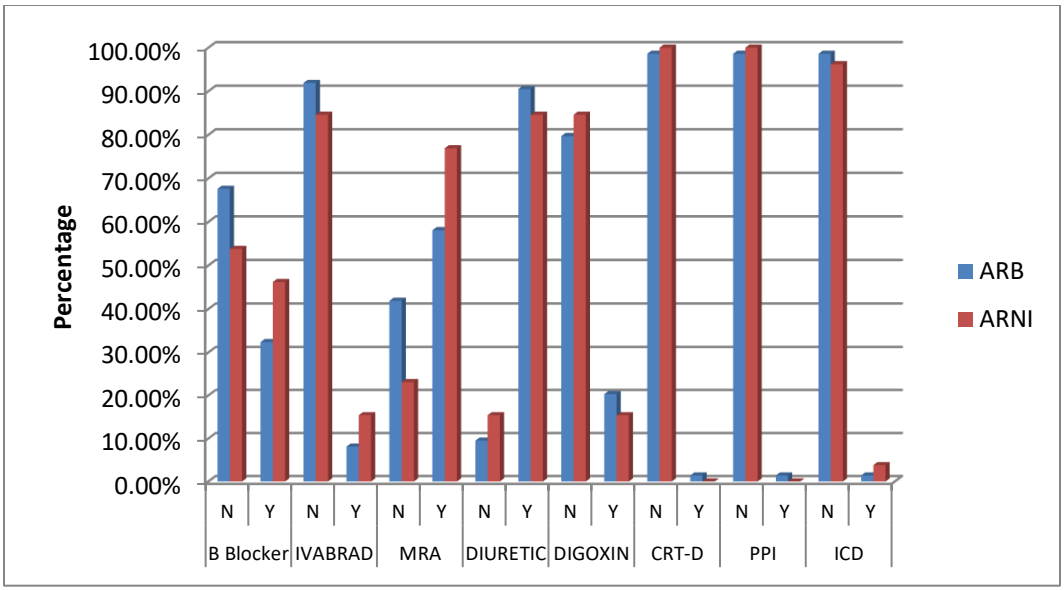


Figure 24: Comparison of baseline medication between both groups.

Table 28: Comparison of adverse affects in both groups.

		Group 1				Total	Chi-square value	p-value
		ARB		ARNI				
DEC. RENAL FUNCTION	N	61	96.8%	25	100.0%	86	0.812	0.367
	Y	2	3.2%	0	0.0%	2		
K+ >5.5	N	60	95.2%	23	92.0%	83	0.350	0.554
	Y	3	4.8%	2	8.0%	5		

Table 28 and figure 25 shows comparison of adverse affects in both groups. Decreased renal function is defined as GFR less than 30ml/min or fall in GFR more than 50% from baseline. Renal dysfunction developed in 2 patients in ARB group and there was no difference regarding frequency of renal dysfunction between both groups with p value 0.367.

Hyperkalemia defined as k+ more than 5.5 occurred in 3 patients in ARB vs 2 patients in ARNI group with no significant difference (p value 0.554) in both groups.

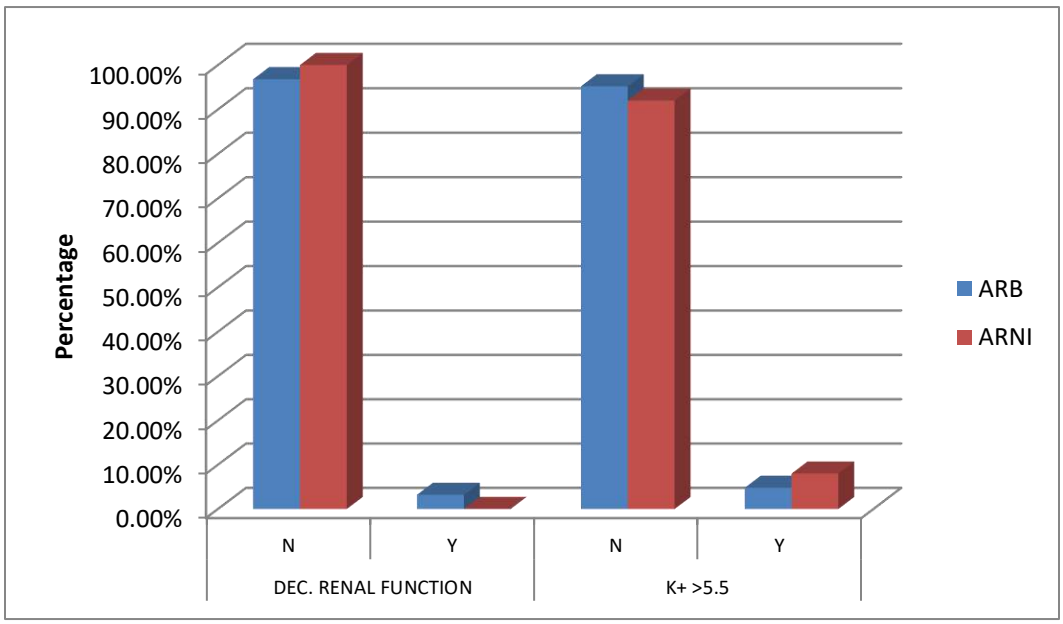


Figure 25: Comparison of adverse affects in both groups.

Table 29: Comparison of Hospitalization and mortality between both groups.

		Group				Total	Chi-square value	p-value
		ARB		ARNI				
HOSP 6-12M	N	56	87.5%	25	96.2%	81	1.538	0.215
	Y	8	12.5%	1	3.8%	9		
MORT 6-12M	N	63	98.4%	25	96.2%	88	0.444	0.501
	Y	1	1.6%	1	3.8%	2		

Table 29 and figure 26 shows comparison of Hospitalization and mortality between both groups. 8 patients hospitalized in ARB group vs 1 patient in ARNI group with no significant difference p value 0.215. Similarly there was no difference I mortality between both groups with insignificant p value 0.501.

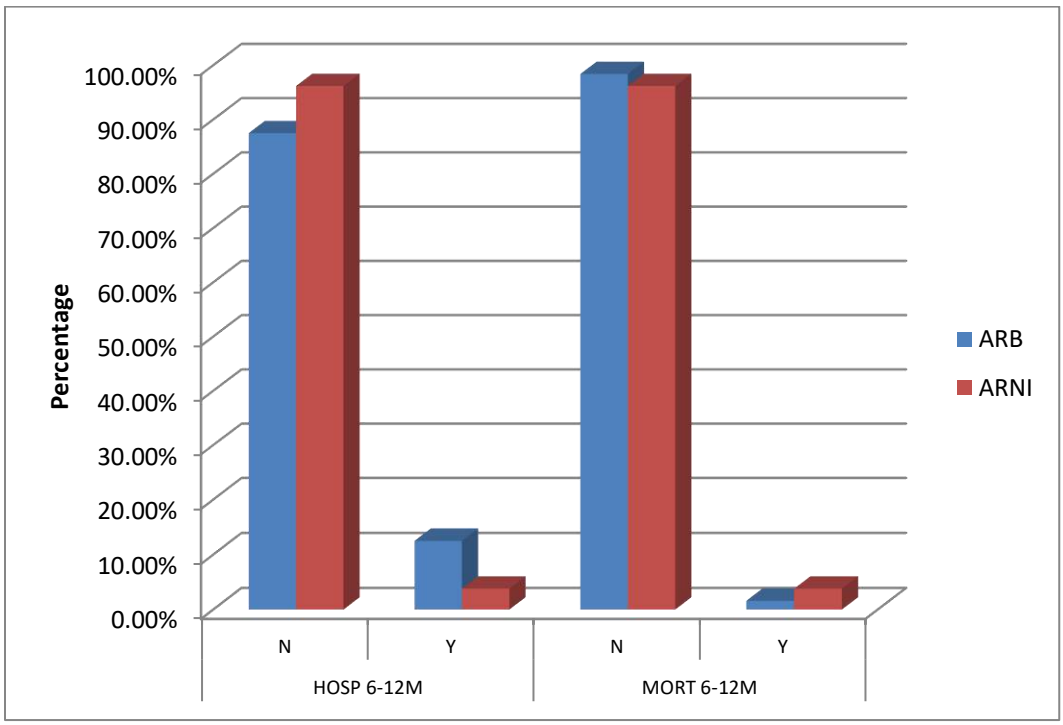


Figure 26: Comparison of Hospitalization and mortality between both groups.

Table 30: Comparison of patients lost to follow up in both groups.

		Group				Total	Chi-square value	p-value
		ARB		ARNI				
Loss to follow up	N	70	94.60%	26	100.00%	96		
	Y	4	5.40%	0	0.00%	4		
Total		74	100.00%	26	100.00%	100	1.464	0.226

Table 30 shows comparison of patients lost to follow up in both groups. 4 patients lost follow up due to ongoing pandemic but there was no significant difference in patients lost to follow up in both groups (p value 0.226).

Table 31: Comparison of clinical and echocardiographic parameters in ARB group patients at 6 and 12 months.

ARB	6 MONTH		12 MONTH		T	p-value	Difference	
	Mean	SD	Mean	SD			Mean	Std. Error
6 MWD	291.02	63.62	291.21	60.67	-0.073	0.942	-0.19	20.59
EF	31.57	7.80	31.95	8.90	-0.569	0.571	-0.38	5.31
LVIDs	48.52	9.48	48.08	9.04	1.073	0.287	0.44	3.29
LVIDd	61.54	11.52	60.89	10.87	1.588	0.117	0.65	3.25
LA	44.67	8.15	44.94	8.02	-.616	0.540	-.270	3.474
MV E/A	1.22	0.47	1.22	0.38	-.192	0.849	-.005	.211
PASP	37.78	12.19	37.84	10.07	-.057	0.955	-.063	8.841
TAPSE	19.95	3.23	19.71	3.52	0.962	0.340	0.24	1.97

Table 31 and figure 27 shows comparison of clinical and echocardiographic parameters in ARB group patients at 6 and 12 months. There was no significant difference in clinical and echocardiographic analysis at 6 and 12 months in ARB group (all p values > .05).

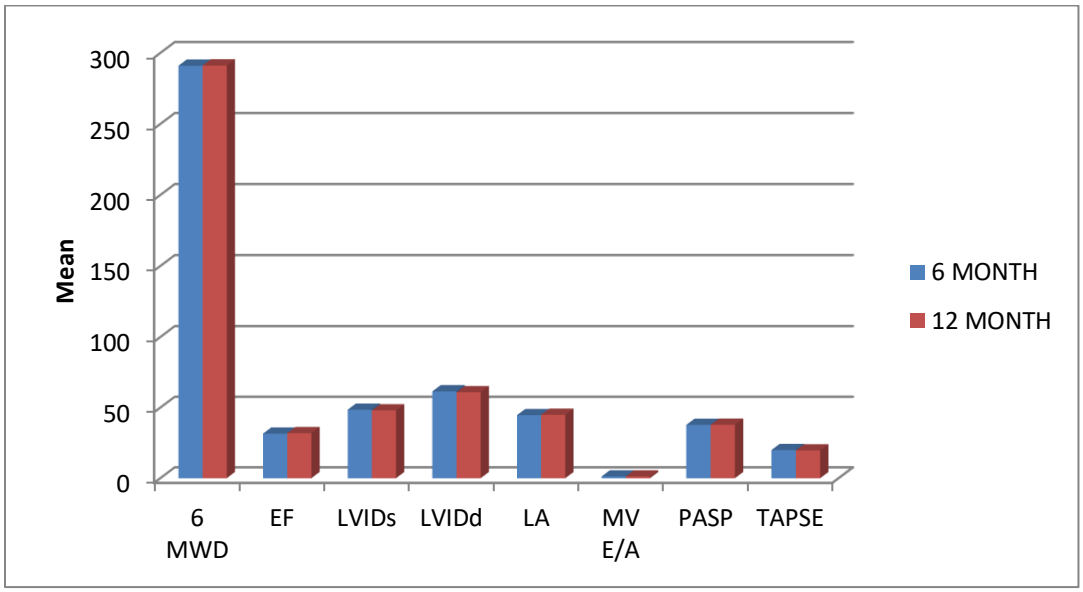


Figure 27: Comparison of clinical and echocardiographic parameters in ARB group patients at 6 and 12 months.

Table 32: Comparison of clinical and echocardiographic parameters in ARNI group patients at 6 and 12 months.

ARNI	6 MONTH		12 MONTH		t	p-value	Difference	
	Mean	SD	Mean	SD			Mean	Std. Error
6 MWD	308.68	52.58	396.00	30.71	-11.814	<.001	-87.32	36.96
EF	29.24	6.15	33.88	7.73	-4.190	<.001	-4.64	5.54
LVIDs	48.32	9.78	45.40	9.48	5.060	<.001	2.92	2.89
LVIDd	61.44	11.03	58.64	10.11	2.017	0.050	2.80	6.94
LA	43.21	9.52	39.79	8.91	2.347	0.028	3.42	7.13
MV E/A	1.07	0.46	1.07	0.37	-0.062	0.951	0.00	0.34
PASP	36.92	11.49	32.80	8.50	2.284	0.032	4.12	9.02
TAPSE	19.04	5.53	21.72	3.25	-3.205	0.004	-2.68	0.84

Table 32 and figure 28 shows comparison of clinical and echocardiographic parameters in ARNI group patients at 6 and 12 months. There is significant improvement in 6 min walk distance at 12 months as compared to 6 months. (p value <0.001). In echocardiographic parameters, significant improvement was seen in ejection fraction, LVIDs, LVIDd, LA diameter, PASP and TAPSE (p value <0.001). In ARNI group, no significant difference was seen in MV E/A (p value 0.951).

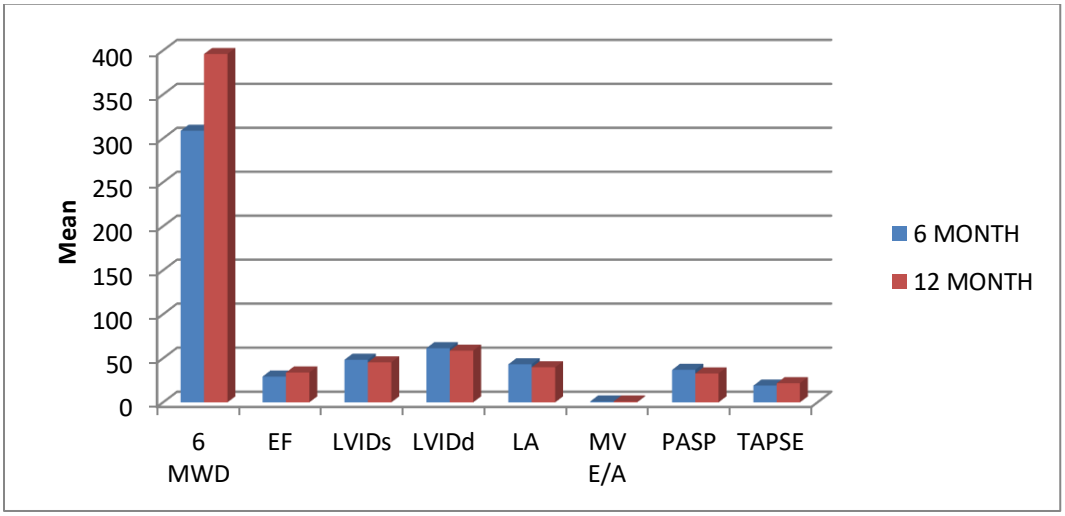


Figure 28: Comparison of clinical and echocardiographic parameters in ARNI group patients at 6 and 12 months.

DISCUSSION

To the best of our knowledge, this is the first of its kind study in the country, studying the effect of sacubitril/valsartan therapy on cardiac remodeling in HFrEF patients previously treated with a maximum tolerated dose of ARB for a sufficient period for neurohormonal modulation. In this study, main findings indicate that switching to sacubitril/valsartan induces incremental reverse remodeling resulting in improvement in ejection fraction which was associated with functional improvement like improvement in NYHA functional class and increase in 6 minute walk distance. Pharmacotherapy remains the cornerstone of therapy for patients with HFrEF. Till now only ACE-I/ARB, beta-blockers, and MRAs have potential for reverse remodeling. Indeed ARBs improve LVEF between1%-4% [52], beta-blockers improve LVEF between 6% [53] and MRAs generally improve LVEF by another 3% [54]. In our study, there is an additional improvement of 4.6% in LVEF after switching patients from ARB to sacubitril/valsartan. The previous studies for the assessment of cardiac remodeling in patients with CHF on ARNI have shown improvement in EF ranging from 3.4%-9.4%. These studies have mostly assessed the elderly population with a mean age above 65. Januzzi et al [44] found 9.4% improvement in EF, Martens et al [43] 5.25%, Almufleh et al [45] 5.09%, Bayard et al [46] 3.4%in HFrEF patients.

Table 33: Comparison of various studies undertaken for the assessment of improvement in EF on ARNI in HFrEF patients.

Source (First Author)	Year	Country	Study Period	Design	No. of Patients on ARNI	Age, Mean ±SD, y	EF Improvement, %
Januzzi	2019	US	2016-2018	Prospective	794	65	9.4
Martens	2018	Belgium	N/A	Prospective	125	66±10	5.2
Almufleh	2017	Canada	2015-2017	Retrospective	48	70±11.1	5.09
Bayard	2019	France	2017-2018	Prospective	52	70±10	3.4
Our Study	2020	India	2019-2020	Prospective	26	60.81±12.54	4.64

Table 33 shows a comparison of various studies done in the recent years in the patients with HFrEF assessing improvement in EF in patients on ARNI in addition to standard medical therapy. Our study finding of increased EF in the HFrEF patients is in line with the previous studies done mainly in the US, Belgium, Canada and France. These studies have been done mostly in the elderly population with a mean age above 65 years of age. Our study had a mean age of 60.8 years and included a relatively younger population as compared to the other studies. In our study, the median (25^{th}-75^{th} percentile) duration of heart failure was 25.5 months (11-44.5 months) indicating sufficient time for neurohormonal blocker uptitration before initiation of sacubitril/valsartan.

Beltran et al [51] evaluated the effects of sacubitril/valsartan on a 30-day six-minute walk test in patients with HFrEF and found a significant increase of 41.8 m in 6 MWT at 30days.Our study also found a significant increase by 87 m at 6 months on ARNI.

Almufleh et al [45] studied effect of ARNI on LV remodeling parameters and found a significant improvements in left ventricular remodeling

parameters including reductions in LVESD (3.36±1.6 mm), LVEDD(2.64±1.1 mm), (all *p* values <.05). Similarly in our study there was reduction in LVIDs by 2.90mm and LVIDd by 2.80 mm with significant p value.

In our study no significant modifications were observed in terms of LV diastolic function parameters which were in line with study done by Bayard et al [46] and it may be due to small sample size and absence of sinus rhythm in 4/25 (16%) patients, so more research is needed to answer this question.

In our study there was significant reduction in PASP by 4.12 mm HG which was comparable to study done by Marten et al [43], reduction in PASP by 4.79 mm HG; Bayard et al [46]; reduction in PASP by 7 mmHg.

Kang et al [47] conducted a study to see effects of ARNI on mitral regurgitation and found significant reduction in EROA; similarly Bayard et al found decrease in severity of MR in ARNI responders. Our study also showed significant reduction in severity of mitral regurgitation in patients on ARNI at 6 months of follow up.

De Vecchis et al [37] conducted a study to compare all cause mortality, heart failure hospitalization and safety outcomes among patients on ARNI as compared to conventional medical therapy and found a significant reduction in mortality by 6.8% in patients taking sacubitril/valsartan vs. 34% in those on conventional therapy (odds ratio [OR] = 0.14; 95% CI: 0.04–0.49). Moreover, there was a 4.5% rate of HF hospitalizations in the sacubitril/valsartan group vs. 59% in the control group (OR = 0.03; 95% CI: 0.01–0.14) but there was no difference in rates of hyperkalemia and rise in serum creatinine in both groups. While in our study there was no difference in mortality, heart failure hospitalization, rates of hyperkalemia and rise in serum creatinine in patients on ARNI vs conventional therapy.

In our study significant reduction in LA diameter was seen by 3.42 mm and it was in line with study conducted by Januzzi et al [44] in which significant reduction in LAVI was seen.

Bayard et al [46] found no significant improvement in RV parameters in their study while in our study significant improvement seen in TAPSE by 2.68 mm. So, more studies are needed to evaluate ARNI effects on RV parameters.

Overall 1 year all cause mortality in our study was 8 % which was comparable to ASIAN HF registry in which overall 1 year mortaliy in South Asia was 8.3%.

Limitations of the study:

1. This was a single centre study.
2. No. of patients on ARNI were less.
3. Shorter duration of follow up. Our analysis might under-estimates the true reverse remodeling response, which could be even higher with longer follow-up.
4. Study was not double blind randomized controlled trial.
5. Lesser dose of ARNI was used in most patients (50 mg bd), only 3 patients were on 100 mg bd.
6. Many other informative echocardiographic assessments were not assessed such as atrial volumes, strain analysis, and tissue Doppler imaging. In addition, the diagnostic acuity of 3D-echocardiography or magnetic resonance imaging can be assessed in such patients.

SUMMARY AND CONCLUSION

The present study was done in total of 100 patients from the period of May 2019 to June 2020 with the aim of assessment of clinical and echocardiographic features in systolic heart failure patients switched from angiotensin receptor blockers to sacubitril/valsartan in OPD/IPD of Hero DMC Heart Institute, Ludhiana, Punjab. All patients were subjected to routine investigations as per protocol and evaluated for clinical and echocardiographic parameters. At baseline 100 patients were taken as per inclusion criteria and followed up for 6 months. The mean age was 61.67 years. The male to female ratio in the study population was 1.85:1, with 65 males and 35 females. The patients with a history of ischemic cardiomyopathy constituted 44% of the study population, while 56% patients had dilated cardiomyopathy. The percent of diabetics were 38% and the hypertensive patients were 44% of the study population. The baseline ejection fraction of the study population was 30.12 % (SD=6.28). The median (25^{th}-75^{th} percentile) duration of heart failure was 25.5 months (11-44.5 months). During 6 months follow up, 6 patients expired and only 94 patients completed follow up at 6^{th} month. These patients were evaluated for 6 MWDT, NYHA functional classification and echocardiographic remodeling parameters and compared with baseline. There was no significant improvement in 6 MWDT and echocardiographic remodeling parameters like EF,LVIDs, LVIDd, LA diameter, MV E/A, PASP, TAPSE and MR severity between baseline and 6 months (all *p* values >.05) but there was significant improvement in NYHA functional class at 6 months as compared to baseline with p value of 0.001. At 6 months patients were given option to switch to ARNI group and only 26 patients opted for ARNI group and 68 patients continued on ARBs. Thus only 27 % (26/94) patients were switched to ARNI group due to cost issue for long term maintenance of therapy. The baseline characteristics of patients in both groups were comparable in relation to age distribution, etiology of HF, baseline comorbidities and baseline therapy. These

patients were followed up for another 6 months and at 1 year again these patients were evaluated for clinical and echocardiographic remodeling parameters. At 1 year there was significant improvement in 6MWDT, NYHA functional class and echocardiographic remodeling parameters like EF,LVIDs, LVIDd, LA diameter, PASP, TAPSE and MR severity in ARNI group as compared to ARB group (all *p* values >.05) but there was no significant improvement in diastolic function and it may be due to small sample size, shorter duration of follow up and absence of sinus rhythm in 4/25 (16%) patients in ARNI group, so more research is needed to answer this question. Regarding adverse effects we found no significant difference in frequency of renal dysfunction and hyperkalemia in both groups. Similarly in our study there was no difference in hospitalization rates and mortality in both groups.

Thus, from our study we conclude that:

1. In HFrEF patients on optimal medical therapy who remain symptomatic, switching from ARB to sacubitril/valsartan induces beneficial cardiac reverse remodeling except diastolic function.
2. Patients on ARNI have also improvement in 6MWD and NYHA functional class.
3. Switching patients on ARNI does not increase incidence of renal dysfunction or hyperkalemia as compared to ARB.
4. Patients switched on ARNI group have not increase in hospitalization rates or mortality as compared to ARB group.
5. Overall 1 year all cause mortality in HFrEF patients is high.

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PROFORMA

Name: GROUP:

Age:

Sex:

MRD No. :

Address:

Chief complaints:

Brief History of Present:

Illness

Past History

DIABETES MELLITUS:

HYPERTENSION:

CKD:

Personal History

Smoker/Non Smoker:

Alcoholic/Non-Alcoholic:

Veg. / non veg:

Medications at baseline:

Signature of Candidate Signature of Supervisor

Family History

Diabetes Mellitus:

Hypertension:

Examination

GPE

Height:

Weight:

Anemia :

Cyanosis :

Jaundice :

Oedema :

JVP-

Pulse :

Blood Pressure :

Respiratory Rate:

Temperature :

System Examination

-Abdomen

-CVS:

-Chest:

-CNS:

Investigations

CBC

FBS/RBS

BNP

ECG

RFT every 2months

Signature of Candidate Signature of Supervisor

	Baseline	2 months	4 months	6 months	8 months	10 months	12 months
Na							
K							
Cl							
Urea							
Creatinine							

	Baseline	6months	1 year
NYHA Class			
6 Minute walk distance			
ECHO Parameters: LV EJECTION FRACTION LV Internal Diameter(systole) LV Internal Diameter(diastole) LA Diameter MV E/A velocity ratio Mitral regurgitation severity PASP TAPSE			

Maximum Tolerated Dose of sacubitril/valsartan:

Signature of Candidate Signature of Supervisor

KEY TO MASTER CHART

Group	
1	ARB
2	ARNI
Etiology of Heart failure	
1	ICMP
2	NICMP
NYHA Class	
1	I
2	II
3	III
4	IV
MR SEVERITY	
1	No
2	Mild
3	Moderate
4	Severe

Sr. No	Group	Name	AGE	SEX	Time since diagnosis of HF(months)	ETIO OF HF	MRD.NO	COMPLAINTS							PAST HISTORY									Baseline THERAPY										BASELINE BNP	BASELINE ECG	BASELINE	2 MONTHS
								CHEST PAIN	DOE	PAPITATIONL	FATIGUE	SYNCOPE	Oedema	no complaint	DM	HTN	CAD	DCMP	COPD	CVA	THYROID	AF	CABG	B Blockers	IVABRADINE	ACEI	ARB	MRA	DIURETICS	DIGOXIN	CRT/CRT-D	PPI	ICD				
1	ARB	JN	86	M	10	NICMP	726222	-	Y	-	-	-	-	-	Y	-	-	Y	-	-	Y	-	-	-	-	-	Y	-	Y	-	-	-	-	103	NSR	1.6	1.4
2	ARB	SK	70	F	11	ICMP	716696	-	Y	Y	-	-	-	-	Y	Y	Y	-	-	-	-	Y	-	Y	-	-	Y	-	-	-	-	-	-	237	intermittent AF	0.9	0.8
3	ARNI	JS	72	M	36	ICMP	218901	-	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	Y	Y	-	-	-	Y	Y	Y	-	-	-	-	846	intermittent AF	0.7	0.8
4	ARB	RG	65	M	24	ICMP	461722	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	1320	NSR	0.4	0.6
5	ARB	SK	60	F	11	NICMP	720265	-	Y	-	-	-	Y	-	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	400	NSR	1.2	1.1
6	ARB	UL	81	F	34	ICMP	635623	-	Y	Y	-	-	-	-	Y	Y	-	-	-	-	-	Y	-	-	-	-	Y	-	Y	-	-	-	-	228	AF/LBBB	1.2	1.1
7	ARB	RK	75	F	8	ICMP	651813	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	Y	-	-	-	654	NSR	1.3	1.1
8	ARB	RK	67	F	22	ICMP	509042	-	Y	-	Y	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	-	-	-	1490	NSR	0.9	0.8
9	ARNI	RS	36	M	34	NICMP	408327	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	854	NSR	0.8	0.9
10	ARB	MS	65	M	10	NICMP	735332	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	456	NSR/IVCD	0.8	0.9
11	ARB	JS	33	M	10	NICMP	687006	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	Y	-	-	-	985	NSR	0.8	0.9
12	ARNI	MS	75	M	8	NICMP	652807	-	Y	Y	-	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	Y	Y	Y	-	-	-	Y	753	AF	0.8	0.9
13	ARB	KS	62	M	8	ICMP	731762	Y	Y	-	-	-	-	-	Y	Y	Y	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	413	NSR	1.2	1.1
14	ARB	MK	50	F	34	ICMP	615021	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	951	NSR	0.7	0.8
15	ARNI	ND	53	M	12	NICMP	735295	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	Y	-	-	-	369	NSR	0.8	0.9
16	ARB	MS	58	M	34	NICMP	235693	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	456	NSR	0.9	1.1
17	ARNI	MS	65	M	44	NICMP	197551	-	Y	-	-	-	Y	-	Y	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	Y	-	-	-	962	NSR/LBBB	0.9	1.1
18	ARNI	SR	78	F	24	NICMP	555435	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	741	NSR	0.6	0.7
19	ARB	GS	70	M	22	NICMP	420533	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	Y	-	-	-	632	NSR	1.4	1.3
20	ARB	NS	44	M	58	ICMP	31611	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	Y	-	Y	-	-	-	-	251	NSR	0.7	0.8
21	ARB	GS	60	M	46	NICMP	300887	-	Y	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	Y	Y	Y	-	-	-	-	475	AF	2.6	2.8
22	ARB	JS	65	M	48	ICMP	201385	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	255	NSR	1.2	1.1
23	ARB	SD	69	M	10	NICMP	726263	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	456	NSR/LBBB	0.7	0.8
24	ARB	JS	58	M	66	NICMP	144618	-	Y	Y	-	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	Y	Y	Y	Y	-	-	-	325	AF	1.8	1.7
25	ARB	RK	69	F	68	NICMP	172207	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	951	NSR	0.8	0.7
26	ARB	JS	50	M	26	ICMP	512493	Y	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	456	NSR/LAFB	1.2	1
27	ARB	CK	48	F	12	NICMP	684841	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	361	NSR	0.7	0.9
28	ARB	MS	55	M	68	NICMP	164160	-	Y	Y	-	-	-	-	Y	Y	-	-	-	Y	-	Y	-	-	-	-	Y	-	Y	Y	-	-	-	753	AF	0.8	0.9
29	ARB	GS	79	M	25	ICMP	513026	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	917	NSR	0.8	0.7
30	ARB	SS	73	M	64	NICMP	148091	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	-	-	-	397	NSR	1.3	1.1
31	ARB	DK	67	F	38	NICMP	196687	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	482	NSR/LBBB	1.2	1.1
32	ARNI	GK	56	F	70	NICMP	153665	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	1306	NSR/LBBB	1.1	0.7
33	ARB	SG	61	M	25	ICMP	520203	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	Y	-	Y	Y	-	-	Y	Y	Y	-	-	-	-	800	NSR	1.2	0.9
34	ARNI	SS	60	M	26	ICMP	568454	Y	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	Y	-	-	-	Y	Y	Y	-	-	-	-	2620	NSR/LBBB	0.8	0.6
35	ARB	TS	62	M	12	ICMP	732863	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	263	NSR	1	0.4
36	ARB	PS	60	M	22	NICMP	592195	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	654	NSR	0.9	0.7
37	ARB	BD	51	F	26	NICMP	418390	-	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	Y	-	1288	PACED	0.9	1
38	ARNI	SS	60	M	28	ICMP	567768	Y	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	403	NSR	0.9	0.8
39	ARNI	AK	76	M	11	ICMP	733611	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	2163	NSR	0.9	0.8
40	ARB	DSR	41	M	11	NICMP	760614	-	Y	-	Y	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	Y	-	-	-	825	NSR	0.8	0.9

			Creatinine					Na+							K+							NYHA CLASS			6 MWD			EF			LVIDs			
Sr. No	Group	Name	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	2M	4M	6M	8M	10M	12M	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE
1	ARB	JN	1.3	-	-	-	-	137	140	142	-	-	-	-	4.2	4	4.1	-	-	-	-	II	-	-	304	-	-	32	-	-	42	-	-	48
2	ARB	SK	1	1.1	0.8	1	0.9	132	136	140	135	136	130	140	4.3	4.2	4.6	4	4.2	4.1	4.1	II	II	II	350	360	360	22	20	22	58	62	59	74
3	ARNI	JS	0.8	1	0.7	1	1.1	141	140	136	131	130	132	138	3.7	3.8	4	4.2	4.1	4	4.3	II	II	II	304	340	400	34	34	28	50	49	48	60
4	ARB	RG	0.5	0.6	0.5	0.6	0.8	138	135	130	136	139	140	135	5.2	3.6	3.9	4	4.1	3.8	3.9	II	II	II	326	320	300	26	28	24	49	53	52	78
5	ARB	SK	1.1	1	1	0.9	1.2	137	136	134	135	130	132	129	4	4.4	4.2	4.1	4.5	3.9	4.1	II	III	III	340	300	290	28	28	26	48	50	51	75
6	ARB	UL	1.1	1	-	-	-	135	136	134	130	-	-	-	4.5	4.4	4.2	4.8	-	-	-	II	II	-	316	328	-	38	35	-	40	42	-	52
7	ARB	RK	1.2	1	1.1	1	0.9	-	130	136	132	128	136	135	5	3.8	4	3.9	4.1	4.2	4	III	II	III	300	356	360	25	24	26	59	60	60	70
8	ARB	RK	0.9	-	-	-	-	139	140	138	-	-	-	-	3.9	4	4.1	-	-	-	-	III	-	-	306	-	-	18	-	-	66	-	-	77
9	ARNI	RS	0.8	0.8	0.7	0.9	0.9	130	136	134	130	125	136	128	4	4.1	4.4	4.8	4.9	5	5.1	III	II	II	320	340	420	22	30	35	63	61	56	70
10	ARB	MS	0.8	1.3	1.4	1.1	1	135	138	134	134	132	128	129	4	3.8	3.9	4.7	4.2	4.1	3.9	IV	iii	II	60	300	320	35	34	35	46	48	43	54
11	ARB	JS	1	3.1	1.4	-	-	138	139	140	139	130	-	-	4	4.1	4	3.8	3.6	-	-	II	II	-	360	440	-	18	25	-	68	60	-	76
12	ARNI	MS	0.5	0.7	0.7	0.7	0.8	139	134	136	140	143	127	140	3.9	4.8	3.9	4.3	4.4	4.4	4.2	III	II	II	290	310	420	24	26	25	49	53	52	74
13	ARB	KS	1.1	1	1.2	0.9	1	138	136	136	140	142	135	139	4	4	4.1	4.3	3.8	3.5	4.8	IV	III	IV	180	270	280	38	36	35	41	45	46	52
14	ARB	MK	0.7	0.7	0.8	0.7	0.8	131	136	134	140	143	135	139	4.5	4.4	4	4.1	4	4.6	4	III	II	II	300	340	320	36	39	55	42	34	32	52
15	ARNI	ND	0.9	1.3	1	1.1	1.2	136	138	140	137	136	140	138	4	4.1	4.4	4.7	4.6	4	4.2	II	II	II	320	330	424	25	28	32	54	49	44	75
16	ARB	MS	1	1	0.9	0.8	1	140	143	138	135	129	145	136	5.3	3.6	3.9	3.9	4	3.8	3.9	III	II	III	270	310	280	25	23	22	56	54	53	66
17	ARNI	MS	1.2	0.8	0.9	0.8	0.7	135	136	140	138	128	129	135	4	4.2	4.4	4.3	4	4.3	4.8	II	II	II	330	360	400	18	15	18	58	70	68	76
18	ARNI	SR	0.9	0.8	0.5	0.8	0.9	140	138	139	136	128	135	136	5.2	3.8	3.6	4.5	4	4.8	4.2	II	II	II	390	340	420	30	25	36	50	48	53	60
19	ARB	GS	1.2	1.4	1.2	1.3	1.4	134	136	134	138	126	128	132	4.9	4.4	4.2	5.4	5	4.8	4.3	II	II	II	300	350	340	24	45	40	50	35	38	70
20	ARB	NS	0.9	-	-	-	-	136	134	130	-	-	-	-	4	4.1	3.8	-	-	-	-	II	-	-	240	-	-	40	-	-	38	-	-	47
21	ARB	GS	2.6	2.4	2.1	2.2	2.5	125	128	130	141	138	135	137	4.6	4.4	4.6	4.5	4.8	4.5	4.9	II	II	II	330	400	400	32	30	45	51	44	34	61
22	ARB	JS	1.1	1.2	1	1	1.1	140	142	144	137	129	130	128	4.5	4.6	4.3	4.6	-	-	-	II	II	-	300	310	-	38	48	-	43	32	-	52
23	ARB	SD	0.6	0.9	0.8	0.7	0.8	138	136	134	130	136	140	141	4	4.2	4.1	4	4.3	4.4	4.9	III	III	III	270	260	254	30	28	26	40	42	44	62
24	ARB	JS	2	2.5	1.9	1.8	2	137	136	130	135	139	142	145	4	4.4	4.6	4.5	4.9	4.7	4.8	III	III	III	240	244	236	20	22	20	50	52	56	74
25	ARB	RK	0.6	0.9	0.9	0.8	1	136	140	142	139	128	129	124	4	4.4	4.8	4.2	4	4.1	4.6	IV	iv	IV	180	128	150	32	45	45	36	35	33	42
26	ARB	JS	1.1	1	1.1	0.9	1	138	136	134	130	135	136	138	4.1	4.1	4	3.8	3.7	4.1	4.3	II	II	III	330	310	290	38	36	35	47	48	47	59
27	ARB	CK	1	0.5	0.6	0.8	0.7	137	136	139	139	130	134	136	4.6	4.4	4.8	4.4	4	4.3	3.9	II	II	II	240	315	320	28	44	50	52	36	30	60
28	ARB	MS	1	1	0.9	0.9	0.9	133	136	140	131	138	137	140	4.6	4.4	4.8	4	4.2	4.3	4.1	IV	III	III	180	280	270	25	23	22	54	55	54	63
29	ARB	GS	0.6	0.7	0.8	0.9	0.8	142	140	141	133	134	136	140	4	4.2	3.6	4.5	3.8	3.7	4.1	II	II	II	300	250	280	35	38	35	42	31	35	45
30	ARB	SS	1.2	1.1	1	1.2	1	134	140	142	145	137	137	139	4.2	4.4	4.1	4.9	5.1	4.8	3.7	II	III	III	320	280	270	28	27	26	48	50	51	65
31	ARB	DK	1	1.3	1	1.1	1	126	130	134	128	130	134	135	4.5	4.1	4.6	6.3	4.9	5	5.3	II	II	III	270	340	336	35	36	32	44	37	40	56
32	ARNI	GK	0.4	1.7	1.5	1.3	1	132	137	143	138	137	138	139	4.2	4.5	4.8	4.8	4.8	5	4.9	III	III	II	270	230	410	25	32	50	55	42	33	63
33	ARB	SG	0.7	2.6	1.8	1.6	1.5	139	144	132	133	132	134	137	4.8	4.4	4.2	6	4.9	5	4.7	II	II	II	330	285	290	28	32	30	54	40	44	64
34	ARNI	SS	0.7	1.2	1.1	1.3	1.5	135	139	142	136	134	135	135	4.4	4.7	4.1	4.7	4.3	4.8	5.7	II	II	II	300	360	418	30	22	34	30	64	60	62
35	ARB	TS	1.2	1	1.1	1.2	1	130	137	131	135	136	138	140	4	4.4	4.1	4	4.3	4.2	5	II	III	III	320	300	296	36	30	32	41	44	45	58
36	ARB	PS	0.4	0.9	0.8	0.9	0.9	131	135	137	140	139	142	129	4	4.4	4.6	4.7	5	4.9	4.2	II	II	II	310	280	276	36	42	38	53	45	48	63
37	ARB	BD	1.1	1	1	0.9	1.1	140	142	138	140	142	143	144	4	4.2	4.2	4.3	4	4.8	4.7	II	III	III	340	284	276	38	35	34	43	46	44	56
38	ARNI	SS	1	1.1	1	0.8	0.7	135	140	138	137	138	140	138	4.4	4.6	4.4	4.4	4.5	4.6	4.8	III	II	II	330	345	410	32	35	42	59	25	23	70
39	ARNI	AK	1	0.7	0.9	0.8	0.6	138	135	140	140	139	138	137	4	3.8	3.9	4.3	4	4.3	4.6	II	II	II	300	350	420	28	32	40	66	49	45	77
40	ARB	DSR	1	1	0.9	1.1	1	135	138	134	140	139	138	137	4	4.2	4.4	4	4.2	4.9	5	II	II	III	360	340	340	22	20	21	60	62	60	77

Sr. No	Group	Name	ECHO PARAMETERS																		DOSE OF ARNI	HOSP 6M	HOSP 6-12M	MORT 6M	MORT 6-12M	ADVERSE EVENTS						Loss to follow up
			LVIDd		LA-DIAMETER			MV E/A			MR SEVERITY			PASP			TAPSE														
			6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR						SYMP. HYPOTN	DEC. RENAL FN	K>5.5	ANGIOEDEMA	OTHER	
1	ARB	JN	-	-	36	-	-	0.8	-	-	mild	-	-	32	-	-	10	-	-	-	-	-	Y	-	-	-	-	-	-	-
2	ARB	SK	76	78	35	36	37	1.3	1.4	1.6	no	no	mild	25	28	24	22	21	22	-	-	Y	-	-	-	-	-	-	-	-	-
3	ARNI	JS	60	70	35	35	50	1.6	1.1	1.5	mod	mod	mild	28	26	20	23	23	18	100	-	-	-	-	-	-	-	-	-	-	-
4	ARB	RG	79	75	45	46	48	1.1	1.2	1.1	no	mild	mild	70	60	50	21	20	21	-	-	-	-	-	-	-	-	-	-	-	-
5	ARB	SK	75	72	48	49	53	1.5	1.6	1.7	mild	mod	mod	25	28	30	21	20	20	-	-	-	-	-	-	-	-	-	-	-	-
6	ARB	UL	54	-	59	60	-	ONLY E	ONLY E	-	mod	mod	-	45	48	-	18	20	-	-	-	-	-	-	-	-	-	-	-	-	y
7	ARB	RK	72	71	60	61	63	1.5	1.6	1.6	sev	sev	sev	70	72	74	21	10	10	-	-	-	-	-	-	-	-	-	-	-	-
8	ARB	RK	-	-	43	-	-	1.3	-	-	mod	-	-	60	-	-	12	-	-	-	Y	-	Y	-	-	-	-	-	-	-	-
9	ARNI	RS	71	72	34	39	37	1	1	1.1	no	no	NO	30	35	35	23	21	23	100	-	-	-	-	-	-	-	-	-	-	-
10	ARB	MS	57	55	40	46	38	1.8	1.7	1.7	mild	mod	mild	56	55	25	20	22	20	-	-	-	-	-	-	-	-	-	-	-	-
11	ARB	JS	72	-	51	50	-	1.1	1	-	sev	no	-	90	50	-	18	21	-	-	-	-	-	-	-	y	-	-	-	-	y
12	ARNI	MS	78	60	42	55	56	1.5	1.5	0.9	no	no	NO	24	28	40	10	8	18	100	-	Y	-	-	-	-	-	-	-	-	-
13	ARB	KS	55	54	42	43	45	1.7	1.8	1.8	mild	mod	mod	50	54	55	24	23	22	-	-	-	-	-	-	-	-	-	-	-	-
14	ARB	MK	41	48	30	28	31	1.1	1.1	1.2	no	no	no	25	25	40	25	20	22	-	-	-	-	-	-	-	-	-	-	-	-
15	ARNI	ND	74	66	40	47	40	0.4	0.4	0.5	no	mild	mild	30	40	45	24	17	20	200	-	-	-	-	-	-	-	-	-	-	-
16	ARB	MS	68	66	52	53	55	1.2	1.3	1.3	mild	mild	mod	30	36	38	24	22	21	-	-	-	-	-	-	-	-	-	-	-	-
17	ARNI	MS	77	74	37	48	40	1.2	1.5	0.7	sev	sev	mod	55	65	40	20	20	17	100	Y	-	-	-	-	-	-	-	-	-	-
18	ARNI	SR	66	64	49	58	56	1.7	1.8	2	sev	sev	sev	32	46	25	14	13	20	100	-	-	-	-	-	-	-	-	-	-	-
19	ARB	GS	53	55	55	42	44	ONLY E	ONLY E	ONLY E	mod	no	mild	65	20	30	24	20	23	-	-	-	-	-	-	-	-	-	-	-	-
20	ARB	NS	-	-	35	-	-	1.3	-	-	mild	-	-	25	-	-	10	-	-	-	-	-	Y	-	-	-	-	-	-	-	-
21	ARB	GS	65	53	65	60	60	ONLY E	ONLY E	ONLY E	sev	mild	no	38	35	40	15	15	15	-	-	-	-	-	-	-	-	-	-	-	-
22	ARB	JS	46	-	37	40	-	1.4	1.5	-	mild	mild	-	60	20	-	18	22	-	-	-	-	-	-	-	-	-	-	-	-	y
23	ARB	SD	65	54	45	46	48	0.7	1.3	1.4	mild	mod	mod	35	38	40	24	22	22	-	-	-	-	-	-	-	-	-	-	-	-
24	ARB	JS	75	74	48	59	51	ONLY E	ONLY E	ONLY E	mod	mod	mod	40	36	35	15	17	14	-	-	Y	-	-	-	-	-	-	-	-	-
25	ARB	RK	35	38	32	28	32	0.5	0.5	0.7	mild	mild	mild	32	30	30	22	22	21	-	-	-	-	-	-	-	-	-	-	-	-
26	ARB	JS	62	61	32	32	34	1.1	1.2	1.3	no	mild	no	36	40	42	22	21	22	-	-	-	-	-	-	-	-	-	-	-	-
27	ARB	CK	48	42	37	36	27	1.3	1.4	1.2	mod	no	no	40	29	23	21	20	22	-	-	-	-	-	-	-	-	-	-	-	-
28	ARB	MS	65	66	45	46	48	ONLY E	ONLY E	ONLY E	mod	mod	sev	45	48	38	18	17	15	-	-	-	-	-	-	-	-	-	-	-	-
29	ARB	GS	40	44	49	34	36	0.8	0.6	0.8	sev	mild	mod	74	20	35	20	20	26	-	-	-	-	-	-	-	-	-	-	-	-
30	ARB	SS	68	70	56	58	60	1.3	1.4	1.4	mild	mod	mod	45	49	50	21	18	17	-	-	-	-	-	-	-	-	-	-	-	-
31	ARB	DK	51	52	46	44	46	0.5	0.6	0.8	no	mod	mod	30	30	35	22	22	20	-	-	-	-	-	-	-	y	-	-	-	-
32	ARNI	GK	50	43	44	40	25	0.6	0.6	0.7	mod	mod	no	55	45	35	22	19	23	100	-	-	-	-	-	-	-	-	-	-	-
33	ARB	SG	68	65	51	45	48	0.3	0.4	0.6	mild	mild	mod	50	30	40	17	14	15	-	-	-	-	-	-	y	y	-	-	-	-
34	ARNI	SS	69	77	45	57	45	1.2	1.3	1.2	mod	mod	mod	25	55	30	12	9	21	100	-	-	-	-	-	-	y	-	-	-	-
35	ARB	TS	65	61	40	42	44	0.5	0.6	0.6	no	mild	mod	35	39	45	20	18	18	-	-	-	-	-	-	-	-	-	-	-	-
36	ARB	PS	59	60	52	47	48	2.4	2.7	1.8	sev	sev	sev	40	40	50	18	17	16	-	-	-	-	-	-	-	-	-	-	-	-
37	ARB	BD	58	60	34	35	36	1.2	1.3	1.3	no	mild	no	30	35	38	20	18	16	-	-	-	-	-	-	-	-	-	-	-	-
38	ARNI	SS	55	53	45	33	31	1.8	2	1.5	mild	mod	NO	40	28	25	22	25	25	100	-	-	-	-	-	-	-	-	-	-	-
39	ARNI	AK	59	56	37	38	-	1.2	1.3	1.1	mild	no	NO	43	27	26	24	17	22	200	-	-	-	-	-	-	-	-	-	-	-
40	ARB	DSR	80	79	48	49	50	1.5	1.6	1.6	mod	mod	sev	28	35	38	22	20	19	-	-	-	-	-	-	-	-	-	-	-	-

Sr. No	Group	Name	AGE	SEX	Time since diagnosis of HF(months)	ETIO OF HF	MRD.NO	COMPLAINTS							PAST HISTORY									Baseline THERAPY										BASELINE BNP	BASELINE ECG	BASELINE	2 MONTHS
								CHEST PAIN	DOE	PAPITATIONL	FATIGUE	SYNCOPE	Oedema	no complaint	DM	HTN	CAD	DCMP	COPD	CVA	THYROID	AF	CABG	B Blockers	IVABRADINE	ACEI	ARB	MRA	DIURETICS	DIGOXIN	CRT/CRT-D	PPI	ICD				
41	ARB	GS	43	M	50	NICMP	193718	-	Y	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	-	-	-	113	NSR	0.9	0.6
42	ARNI	BS	45	M	12	NICMP	740875	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	Y	-	-	-	963	NSR/LBBB	0.9	1.1
43	ARNI	BS	59	M	9	ICMP	756088	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	941	NSR/IVCD	0.9	1
44	ARB	KS	55	M	8	ICMP	756091	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	1750	NSR/LBBB	1	1.1
45	ARNI	KS	42	M	10	NICMP	650705	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	740	NSR	0.9	1.1
46	ARB	SS	53	M	12	NICMP	727996	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	1460	NSR	0.9	1
47	ARNI	HS	50	M	25	NICMP	417898	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	251	NSR	0.6	0.4
48	ARB	Sk	46	M	7	NICMP	720695	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	3170	NSR	1.2	0.9
49	ARB	MS	65	M	11	ICMP	735332	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	Y	-	-	-	1988	NSR/IVCD	1	1.2
50	ARB	ND	52	M	12	NICMP	735295	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	863	NSR	1.1	0.9
51	ARB	BK	60	F	12	NICMP	735664	-	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	473	NSR	1.2	1
52	ARB	JK	60	F	30	NICMP	502614	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	Y	-	Y	Y	Y	-	-	-	-	656	NSR	0.6	0.8
53	ARNI	SS	80	M	11	ICMP	733981	Y	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	656	NSR	1.2	1.1
54	ARB	JK	54	M	28	NICMP	638506	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	-	-	-	-	Y	658	NSR/BIFASCICULAR BLOCK	0.9	0.8
55	ARB	HR	70	M	38	ICMP	355872	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	922	NSR	1	1.1
56	ARB	KK	65	F	48	NICMP	196527	-	Y	-	Y	-	-	-	Y	-	-	-	-	-	Y	-	-	-	-	-	Y	-	Y	Y	-	-	-	1120	NSR/LAFB	0.9	0.8
57	ARNI	RP	70	F	24	NICMP	621301	-	Y	Y	-	-	-	-	Y	Y	-	-	-	-	-	Y	-	Y	-	-	Y	Y	Y	-	-	-	-	1190	AF	1.6	1.4
58	ARB	RR	62	F	65	NICMP	173108	-	Y	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	Y	-	Y	-	-	-	-	1459	AF	1	0.9
59	ARB	HK	70	F	12	ICMP	737223	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	1720	NSR	1.1	1
60	ARB	MS	76	M	56	ICMP	73230	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	799	NSR	0.60.7	0.8
61	ARNI	NL	53	M	11	ICMP	736074	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	654	NSR	1.1	1
62	ARB	DK	71	M	36	ICMP	315025	Y	Y	Y	-	-	-	-	Y	Y	-	-	-	Y	-	Y	-	Y	-	-	Y	Y	Y	Y	-	-	-	1510	AF	0.6	0.4
63	ARB	CS	60	M	10	ICMP	735273	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	1236	NSR	0.9	0.4
64	ARB	NK	74	F	9	ICMP	735970	-	-	-	-	-	-	-	Y	Y	-	-	-	-	-	-	Y	-	-	-	Y	Y	Y	-	-	-	-	903	NSR/LAFB	0.7	0.6
65	ARB	SP	54	M	49	ICMP	36947	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	2145	NSR	1	0.7
66	ARB	SS	78	M	38	ICMP	267085	Y	Y	-	-	-	-	-	Y	-	-	-	-	Y	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	355	NSR/LBBB	0.8	0.9
67	ARB	BK	73	F	10	ICMP	740697	Y	-	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	470	NSR/IVCD	1	1
68	ARNI	PK	73	F	37	NICMP	351337	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	1930	NSR/LBBB	0.9	0.70.4
69	ARB	AK	66	M	49	NICMP	199666	-	Y	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	-	Y	-	Y	-	-	-	-	789	AF	1.5	1.2
70	ARB	JM	73	M	26	ICMP	464145	Y	-	-	-	-	-	-	Y	-	-	-	Y	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	174	NSR	0.8	0.4
71	ARB	KS	70	F	39	ICMP	340609	-	Y	-	-	-	-	-	Y	-	-	-	-	Y	-	-	Y	-	-	-	Y	Y	-	-	-	-	-	544	NSR/LBBB	0.6	0.4
72	ARB	BS	54	M	24	NICMP	431231	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	-	-	-	110	NSR/LBBB	0.8	0.6
73	ARNI	RS	47	F	54	NICMP	183440	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	-	-	-	-	963	NSR	0.5	0.7
74	ARB	SL	56	M	10	NICMP	759034	-	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	570	NSR	0.7	0.8
75	ARB	VK	59	M	68	ICMP	46491	-	Y	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	-	Y	Y	Y	Y	-	-	-	1400	NSR/RBBB	0.9	0.6
76	ARB	RP	56	M	26	ICMP	630926	-	-	-	-	-	-	-	Y	Y	-	-	-	Y	-	-	-	Y	-	-	Y	-	Y	-	-	-	-	481	NSR	1.4	1.3
77	ARNI	H	70	M	38	ICMP	206775	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	366	NSR	0.6	0.7
78	ARNI	SK	50	F	64	NICMP	65782	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	899	NSR	1	1.1
79	ARB	PK	61	M	65	ICMP	45492	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	Y	-	-	-	-	751	NSR	0.8	0.7
80	ARB	GS	71	M	70	NICMP	150826	-	Y	Y	-	-	-	-	-	Y	-	-	-	-	-	Y	-	-	-	-	Y	Y	Y	-	-	-	-	3470	AF	1.1	1

			Creatinine					Na+							K+							NYHA CLASS			6 MWD			EF			LVIDs			
Sr. No	Group	Name	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	2M	4M	6M	8M	10M	12M	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE
41	ARB	GS	0.8	0.9	1	1	0.8	140	146	138	137	138	139	141	4.5	4.4	4.2	4.1	4	3.9	3.8	II	II	III	330	310	320	32	28	29	49	52	52	61
42	ARNI	BS	1	0.8	1	1.1	0.8	138	136	135	139	140	142	139	4.3	4	4.4	4.8	3.7	4	4	II	II	II	310	320	400	23	30	36	49	54	50	56
43	ARNI	BS	1.1	0.8	0.9	1	1.4	135	136	138	136	138	139	140	4	3.8	3.7	4.5	4	4.1	4.3	II	II	II	370	380	424	33	36	32	54	45	46	65
44	ARB	KS	1.2	0.8	1.2	1	-	140	142	141	137	138	137	-	4	4.4	4.3	4.2	4.1	4.9	-	II	II	-	356	370	-	38	45	-	52	48	-	64
45	ARNI	KS	1.2	0.9	1.3	1	0.9	140	138	136	139	134	132	130	3.8	3.6	4	4.3	4.6	4.7	5.2	II	II	II	360	420	440	32	37	43	59	50	46	68
46	ARB	SS	1.1	-	-	-	-	135	136	140	-	-	-	-	4	4.1	4.4	-	-	-	-	IV	IV	-	180	120	-	27	-	-	44	-	-	51
47	ARNI	HS	0.7	0.9	1	1.1	0.9	136	139	136	138	140	142	138	4.1	4.5	4.8	4.3	4.9	5	4.3	II	II	II	312	330	412	35	30	32	49	42	40	59
48	ARB	Sk	1.1	1	1.2	0.8	1	134	137	141	134	135	139	135	4.4	4.8	4.6	4.8	4.6	4.9	3.8	II	II	III	312	300	280	20	18	18	51	54	53	70
49	ARB	MS	0.9	1	1.1	1	0.9	139	136	141	140	138	137	140	4.3	4.7	4.9	3.9	3.5	4	4.2	iv	iv	iv	180	150	124	35	34	32	46	50	51	54
50	ARB	ND	1	1	0.8	1.2	1.1	138	139	142	135	132	139	140	4.3	4.5	4.7	4.6	4.3	4.9	4.8	II	II	II	320	326	330	25	22	22	60	62	60	68
51	ARB	BK	1	1.1	1	1.2	1	137	135	138	137	130	128	129	4.8	4.4	4	4.4	4.9	5	4.8	IV	III	III	152	296	280	18	18	20	60	61	59	76
52	ARB	JK	0.7	0.5	0.8	0.7	0.9	137	141	144	137	138	130	129	4.2	4.5	4.2	4.3	4	4.8	4.8	II	III	II	272	260	300	20	18	18	65	66	65	76
53	ARNI	SS	1	1.4	1.2	1.1	1	133	137	141	139	135	138	137	4.1	4.6	4.7	3.9	4	4.5	4.9	IV	iii	IIi	160	260	356	37	37	42	48	46	40	59
54	ARB	JK	0.9	1	1.2	0.8	1	137	136	134	130	128	135	138	4.1	4.3	4	4.2	4.3	4.9	5	II	II	III	330	320	296	28	26	25	54	56	55	70
55	ARB	HR	0.9	1.2	1	0.9	1	138	145	138	134	136	137	138	4.7	4.8	4.4	4.9	5	4.8	4.5	II	II	III	312	300	284	33	32	30	53	55	54	65
56	ARB	KK	1	1	0.8	1.3	1	135	136	134	132	131	131	129	4.3	4	4.4	4	4.3	4.7	4.3	IV	iv	IV	180	140	150	35	32	34	35	38	36	42
57	ARNI	RP	1.2	1.7	1.4	1.5	1.3	137	144	142	141	140	135	136	4.4	4	4.8	4.5	4	4.1	4.3	III	III	II	250	210	360	35	21	23	37	42	42	51
58	ARB	RR	0.8	1	1.1	1	1.2	139	135	142	136	134	138	136	4.5	4.6	4.8	4	4.3	4.9	5	III	II	III	200	260	198	32	30	30	40	45	44	51
59	ARB	HK	1.1	-	-	-	-	133	140	143	-	-	-	-	5.3	4.7	4.8	-	-	-	-	III	-	-	-	-	-	36	-	-	33	-	-	50
60	ARB	MS	0.9	1	1.2	1.1	1	133	138	141	140	138	137	138	4.2	4.6	4.5	4.6	4.7	3.5	3.6	II	III	III	320	284	270	38	35	36	42	45	46	52
61	ARNI	NL	0.6	1.6	1.3	1.4	1.3	141	136	132	134	130	138	136	3.9	4.5	4.1	4.3	4	3.9	4.2	III	II	II	270	300	392	38	35	42	45	38	36	56
62	ARB	DK	0.5	0.9	0.8	0.7	0.8	140	133	132	130	128	129	130	4.1	4	4.2	4	3.6	3.8	4.2	II	III	II	332	254	300	36	34	32	45	50	48	54
63	ARB	CS	0.7	0.8	0.7	0.9	0.8	137	143	137	130	134	131	137	4	4.2	4.6	4.9	3.8	5	4.8	II	II	II	360	350	354	26	30	60	49	48	32	57
64	ARB	NK	0.7	0.6	0.9	1	0.8	132	136	142	140	142	146	139	4.3	4.7	4.5	4.7	4.9	5	4.5	II	II	II	374	360	354	35	44	40	49	28	34	57
65	ARB	SP	0.6	1	0.9	1.1	1	132	136	134	130	134	136	134	4.6	4.8	4.4	4.3	4.8	5	5.2	IV	III	III	180	240	230	22	20	18	68	66	65	75
66	ARB	SS	1	-	-	-	-	124	130	136	-	-	-	-	3.9	4	4.4	-	-	-	-	IV	-	-	126	-	-	30	-	-	47	-	-	60
67	ARB	BK	1.1	1.2	1.2	1.1	1	132	140	138	130	128	130	134	4.5	4.4	4	3.7	3.9	3.5	4	IV	iv	IV	190	140	150	38	36	35	47	50	51	58
68	ARNI	PK	0.4	1.1	-	-	-	131	135	142	139	-	-	-	4	4.1	4.4	4.6	-	-	-	IV	III	-	80	290	-	30	32	-	55	54	-	64
69	ARB	AK	1.1	1	1.2	1.1	1	144	140	146	136	138	140	142	4.2	4.6	4.8	4.2	4.9	4.3	3.9	II	II	II	304	311	310	38	34	35	54	56	55	67
70	ARB	JM	0.7	0.8	0.9	0.8	0.8	136	131	135	138	140	142	138	4	4.2	4.4	4	4.6	4.7	3.7	IV	III	IV	140	200	210	34	32	32	48	50	48	62
71	ARB	KS	0.7	0.8	0.9	0.8	0.6	135	142	143	137	140	139	136	4.3	4.6	4.8	4	3.8	4.5	4.3	II	III	III	318	240	234	38	36	35	44	46	46	54
72	ARB	BS	0.4	0.5	0.8	0.9	1	140	132	136	138	145	138	136	4	4.2	4.4	4.1	4.8	4.8	4.7	III	III	III	280	200	196	18	16	18	62	61	60	78
73	ARNI	RS	0.6	0.8	0.9	0.8	0.9	137	139	142	143	149	138	139	4.2	4.5	4.8	4	4.6	4.8	4.7	IV	III	IIi	114	210	346	26	26	22	55	60	52	70
74	ARB	SL	0.9	0.8	1	1.1	1	132	135	130	130	134	136	132	4	4.4	4	4.5	4.9	4.7	4.6	II	III	III	342	300	306	30	28	28	50	54	52	58
75	ARB	VK	0.8	0.9	-	-	-	140	144	142	140	-	-	-	5.1	3.8	3.7	3.8	-	-	-	II	ii	-	237	240	-	28	29	-	52	53	-	61
76	ARB	RP	1.2	1.5	1.3	1.2	1	141	140	142	133	135	136	137	4.7	4.4	4.6	6.2	4	4.3	4.8	II	II	II	380	430	394	36	38	35	44	29	35	58
77	ARNI	H	0.8	1.26	1.2	1	1.2	140	135	136	137	134	139	137	4.4	4.2	4.1	5.6	5.1	5	-	IV	iii	II	180	268	360	33	34	33	46	45	43	53
78	ARNI	SK	0.9	1.1	1	1.3	0.9	140	135	138	126	130	132	137	4	4.4	4.1	5	4.6	4.6	3.8	III	II	II	240	310	416	25	30	30	55	35	35	64
79	ARB	PK	0.9	1	1.2	1	1.2	135	133	138	130	134	135	136	4.5	4.4	4.2	4.2	4.3	4.8	4	II	II	II	420	400	390	35	32	34	51	55	54	62
80	ARB	GS	1.1	0.9	1	1.1	1.2	128	130	134	134	136	138	138	5	3.9	4	4.2	4.3	4.5	4.8	II	II	II	330	326	318	22	30	40	41	44	43	64

Sr. No	Group	Name	ECHO PARAMETERS																		DOSE OF ARNI	HOSP 6M	HOSP 6-12M	MORT 6M	MORT 6-12M	ADVERSE EVENTS					Loss to follow up
			LVIDd		LA-DIAMETER			MV E/A			MR SEVERITY			PASP			TAPSE														
			6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR						SYMP. HYPOTN	DEC. RENAL FN	K>5.5	ANGIOEDEMA	OTHER	
41	ARB	GS	64	65	46	47	49	1.3	1.4	1.4	mild	mild	mild	25	28	30	22	21	20	-	-	-	-	-	-	-	-	-	-	-	-
42	ARNI	BS	63	59	48	46	44	1.3	1.2	1	mild	mod	NO	30	20	22	24	22	25	100	-	-	-	-	-	-	-	-	-	-	-
43	ARNI	BS	53	65	38	30	40	1.2	1.2	1.3	no	no	mild	25	20	30	25	21	25	100	-	-	-	-	-	-	-	-	-	-	-
44	ARB	KS	56	-	45	40	-	1.1	1.1	-	mild	no	-	25	24	-	18	24	-	-	-	-	-	-	-	-	-	-	-	-	y
45	ARNI	KS	54	55	45	25	23	0.6	1	1	no	no	NO	25	35	38	22	20	24	100	-	-	-	-	-	-	-	-	-	-	-
46	ARB	SS	-	-	39	-	-	1.3	-	-	no	-	-	30	-	-	12	-	-	-	-	-	Y	-	-	-	-	-	-	-	-
47	ARNI	HS	62	58	35	39	40	0.8	0.6	0.8	no	no	no	25	25	20	18	18	19	100	-	-	-	-	-	-	-	-	-	-	-
48	ARB	Sk	78	73	46	48	50	1.2	1.3	1.3	mod	mod	sev	45	48	50	11	10	7	-	-	-	-	-	-	-	-	-	-	-	-
49	ARB	MS	57	58	40	42	38	1.5	1.6	1.7	mod	mod	mod	50	52	53	20	18	20	-	-	-	-	-	-	-	-	-	-	-	-
50	ARB	ND	70	70	40	43	40	0.3	0.4	0.5	mild	mod	mod	20	28	35	22	21	20	-	-	-	-	-	-	-	-	-	-	-	-
51	ARB	BK	80	77	42	44	38	1.4	1.5	1.6	mod	sev	sev	60	60	48	24	22	23	-	-	-	-	-	-	-	-	-	-	-	-
52	ARB	JK	78	79	61	62	58	1.5	1.6	1.6	SEV	sev	sev	40	45	46	25	24	22	-	-	-	-	-	-	-	-	-	-	-	-
53	ARNI	SS	52	45	38	40	38	1	0.7	0.8	mild	mod	mild	25	30	25	20	21	24	100	-	-	-	-	-	-	-	-	-	-	-
54	ARB	JK	79	79	41	43	45	1.4	1.5	1.6	NO	mod	mod	22	35	45	20	18	17	-	-	-	-	-	-	-	-	-	-	-	-
55	ARB	HR	68	67	37	39	41	0.8	0.9	0.8	no	mild	mod	25	28	35	22	22	20	-	-	-	-	-	-	-	-	-	-	-	-
56	ARB	KK	45	46	60	60	61	1.3	1.4	1.4	no	mild	mild	26	29	40	24	23	23	-	-	-	-	-	-	-	-	-	-	-	-
57	ARNI	RP	68	60	60	55	40	ONLY E	ONLY E	ONLY E	no	mild	mild	70	50	48	20	30	24	200	Y	-	-	-	-	-	-	-	-	-	-
58	ARB	RR	53	52	46	48	50	ONLY E	ONLY E	ONLY E	mild	mod	sev	20	35	35	22	20	16	-	-	-	-	-	-	-	-	-	-	-	-
59	ARB	HK	-	-	51	-	-	1.4	-	-	mod	-	-	60	-	-	12	-	-	-	-	-	Y	-	-	-	-	-	-	-	-
60	ARB	MS	54	53	38	39	43	0.8	0.8	0.9	mild	mild	mild	30	32	35	22	21	20	-	-	-	-	-	-	-	-	-	-	-	-
61	ARNI	NL	45	43	44	28	25	0.9	1.1	1	no	mild	no	22	25	22	22	23	25	100	-	-	-	-	-	-	-	-	-	-	-
62	ARB	DK	59	58	44	46	48	ONLY E	ONLY E	ONLY E	mod	mod	mod	50	54	55	25	24	24	-	-	-	-	-	-	-	-	-	-	-	-
63	ARB	CS	55	48	40	44	43	0.9	0.8	0.7	no	no	NO	28	32	25	25	23	22	-	-	-	-	-	-	-	-	-	-	-	-
64	ARB	NK	44	50	30	40	45	1.1	1.2	1.3	mild	mild	mild	24	40	42	22	21	20	-	-	-	-	-	-	-	-	-	-	-	-
65	ARB	SP	78	80	37	38	41	1.3	1.4	1.5	no	mod	mod	20	35	48	25	24	23	-	Y	-	-	-	-	-	-	-	-	-	-
66	ARB	SS	-	-	41	-	-	0.6	-	-	no	-	-	30	-	-	10	-	-	-	-	-	Y	-	-	-	-	-	-	-	-
67	ARB	BK	60	59	46	49	53	1.1	1.2	1.3	sev	mod	mod	35	36	48	25	20	25	-	Y	Y	-	-	-	-	-	-	-	-	-
68	ARNI	PK	65	-	48	48	-	1.6	1.6	-	mod	mod	-	30	50	-	15	19	-	100	-	-	-	Y	-	-	-	-	-	-	-
69	ARB	AK	70	70	53	55	56	ONLY E	ONLY E	ONLY E	mod	mod	mod	35	38	40	22	21	20	-	-	-	-	-	-	-	-	-	-	-	-
70	ARB	JM	65	66	51	54	56	2.3	2.1	2	mod	mod	mod	40	45	40	25	24	23	-	-	-	-	-	-	-	-	-	-	-	-
71	ARB	KS	58	56	44	46	48	0.9	0.8	0.9	mild	mild	mod	40	42	36	20	18	18	-	-	-	-	-	-	-	-	-	-	-	-
72	ARB	BS	79	78	48	50	52	1.1	1.2	1.3	mod	mod	mod	50	55	45	17	16	16	-	-	-	-	-	-	-	-	-	-	-	-
73	ARNI	RS	71	60	43	49	53	1.3	1.5	1.8	mild	mod	mod	35	40	30	16	17	17	100	Y	-	-	-	-	-	-	-	-	-	-
74	ARB	SL	60	60	35	38	40	1.5	1.6	1.6	no	no	mild	30	34	35	22	21	20	-	-	-	-	-	-	-	-	-	-	-	-
75	ARB	VK	60	-	40	39	-	1.2	1.3	-	no	no	-	26	28	-	13	21	-	-	-	Y	-	Y	-	-	-	-	-	-	-
76	ARB	RP	57	58	47	40	42	0.8	0.7	0.8	mild	mild	mild	30	15	20	24	19	23	-	-	-	-	-	-	-	y	-	-	-	-
77	ARNI	H	52	52	28	41	38	0.8	0.6	0.6	no	mild	no	32	35	35	18	18	20	100	-	-	-	-	-	-	y	-	-	-	-
78	ARNI	SK	40	48	39	41	40	1.1	0.5	1.1	mild	mild	no	50	30	28	18	18	20	100	-	-	-	-	-	-	-	-	-	-	-
79	ARB	PK	65	64	49	51	53	0.3	0.4	0.5	no	mod	mod	30	40	30	14	13	12	-	-	-	-	-	-	-	-	-	-	-	-
80	ARB	GS	68	60	56	48	46	ONLY E	ONLY E	ONLY E	mod	mod	mod	50	54	30	22	20	21	-	-	Y	-	-	-	-	-	-	-	-	-

Sr. No	Group	Name	AGE	SEX	Time since diagnosis of HF(months)	ETIO OF HF	MRD.NO	COMPLAINTS							PAST HISTORY									Baseline THERAPY										BASELINE BNP	BASELINE ECG	BASELINE	2 MONTHS
								CHEST PAIN	DOE	PAPITATIONL	FATIGUE	SYNCOPE	Oedema	no complaint	DM	HTN	CAD	DCMP	COPD	CVA	THYROID	AF	CABG	B Blockers	IVABRADINE	ACEI	ARB	MRA	DIURETICS	DIGOXIN	CRT/CRT-D	PPI	ICD				
81	ARB	RK	59	M	9	ICMP	753885	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	-	Y	-	-	-	-	269	NSR	0.7	0.9
82	ARB	HK	52	F	40	NICMP	243492	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	-	Y	-	-	-	-	1590	NSR	0.9	1
83	ARB	GS	71	M	69	NICMP	148488	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	-	Y	Y	-	-	-	677	NSR	1	0.9
84	ARB	HK	64	F	72	NICMP	148173	-	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	Y	-	Y	-	Y	-	-	-	-	922	NSR	0.8	0.9
85	ARB	KL	60	M	10	ICMP	651921	Y	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	1157	NSR	0.9	1
86	ARB	PP	57	M	10	NICMP	752020	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	1250	NSR/IVCD	1	1.1
87	ARB	KD	67	F	9	ICMP	697975	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	860	NSR/LBBB	1.1	1
88	ARB	SS	67	M	35	NICMP	389729	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	-	Y	-	-	-	-	1069	NSR	1.1	1
89	ARB	UM	66	F	29	NICMP	420936	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	-	-	-	-	703	NSR	0.7	0.8
90	ARB	KK	62	F	46	ICMP	177256	Y	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	-	-	-	-	983	NSR	0.9	0.9
91	ARB	K	68	F	10	ICMP	765630	Y	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	-	Y	-	-	-	-	1640	NSR	0.9	0.9
92	ARNI	LK	57	F	64	ICMP	163176	Y	Y	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	990	NSR	0.8	0.9
93	ARNI	M	53	M	36	ICMP	472945	-	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	Y	-	-	-	1020	NSR	0.8	1
94	ARB	UJ	60	F	9	NICMP	772818	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	-	-	-	-	66	NSR	0.8	1.1
95	ARNI	DS	61	M	64	NICMP	169354	-	Y	-	-	-	-	-	Y	Y	-	-	-	-	-	-	-	Y	-	-	Y	Y	-	-	-	-	-	321	NSR	0.8	0.9
96	ARB	RR	57	F	70	NICMP	153891	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	Y	-	-	43	PACED	0.9	0.8
97	ARB	AS	55	M	9	NICMP	777610	-	Y	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	Y	-	-	Y	Y	Y	-	-	-	-	481	NSR	0.9	1.1
98	ARNI	AK	83	F	8	NICMP	713206	-	Y	Y	-	-	-	-	Y	Y	-	-	-	-	-	Y	-	-	-	-	Y	-	Y	-	-	-	-	98	AF	0.8	1.2
99	ARNI	MS	57	M	12	NICMP	801457	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	-	-	-	-	220	NSR	0.4	0.3
100	ARB	NK	62	F	6	NICMP	900828	-	Y	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	-	Y	-	Y	-	-	-	-	385	NSR	0.9	0.9

			Creatinine					Na+							K+							NYHA CLASS			6 MWD			EF			LVIDs			
Sr. No	Group	Name	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	2M	4M	6M	8M	10M	12M	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE
81	ARB	RK	1.1	0.9	1	1.4	1	138	136	140	140	142	130	132	4	4.1	4.4	4.3	4.9	3.8	3.9	II	II	II	360	328	330	38	35	36	37	41	40	47
82	ARB	HK	1.1	1	0.7	0.8	0.9	140	138	135	130	132	135	135	4	4.1	4.4	4	3.8	3.7	4.1	II	III	II	330	280	314	22	20	22	58	60	61	70
83	ARB	GS	0.8	0.6	0.9	1	1.1	138	136	135	136	134	135	134	4	4.4	4.2	3.9	3.7	4	4.2	II	III	II	390	346	370	38	36	35	40	45	46	51
84	ARB	HK	1	0.9	1	1.1	0.8	140	138	136	136	128	129	130	4	3.6	3.8	4.3	4.2	3.8	3.7	IV	III	IV	180	190	200	30	30	28	54	55	56	63
85	ARB	KL	1.1	0.6	0.9	1.2	1	142	136	138	134	136	134	137	4.2	4.4	3.8	3.8	3.7	4	4.3	II	II	II	346	330	316	37	35	34	50	54	53	62
86	ARB	PP	1	0.7	0.8	1	1.1	137	140	136	134	139	138	137	4.6	4.4	4.2	4.3	4.5	4.8	5	II	II	II	346	326	328	22	22	20	63	64	63	71
87	ARB	KD	0.9	0.8	1	0.9	1	130	136	138	135	136	134	130	4.2	4.4	4.6	5.2	5.3	5	4.8	II	II	II	368	350	346	34	32	30	39	43	42	49
88	ARB	SS	0.9	1.5	1.3	1.2	1	140	136	138	137	134	135	136	4	4.4	3.8	4.5	5	4.9	4.6	II	III	III	356	240	310	20	48	45	52	57	56	64
89	ARB	UM	0.9	0.8	1	1.1	1	137	136	135	136	128	140	136	3.9	4	4.2	5	4.7	4	4.3	IV	III	III	180	240	254	30	42	40	50	36	38	59
90	ARB	KK	1.1	1	0.8	1.1	1	140	138	145	135	136	139	140	4	4.4	3.8	4.6	4.4	4.9	5	II	III	II	340	285	316	35	32	33	47	50	50	56
91	ARB	K	0.8	0.9	1	1	1.1	137	140	136	134	136	139	132	5.2	3.6	3.9	4.4	4.6	5	4.8	II	II	II	360	354	346	32	32	30	45	48	47	54
92	ARNI	LK	1	1.2	1.1	1	1.1	140	136	135	132	132	128	129	4	4.4	4.2	4.7	4.8	4.9	5	III	III	II	250	280	388	26	26	29	49	55	51	75
93	ARNI	M	1.1	1	0.9	1	0.9	136	138	140	138	130	132	129	5.3	4.2	4.1	4.9	5	5.3	5.2	IV	iii	II	180	250	364	26	15	25	58	58	54	72
94	ARB	UJ	1	0.9	1	1	0.9	140	135	136	132	139	138	137	4	4.1	3.8	3.9	4.3	4.5	4.2	II	II	II	380	360	354	38	36	35	59	60	58	47
95	ARNI	DS	1	1.2	1.1	1	0.8	140	142	138	137	136	138	135	4	4.1	3.8	4.5	4.3	4.2	4.9	III	iii	IIi	300	280	310	28	35	40	50	40	38	58
96	ARB	RR	0.9	0.6	0.9	1	1.2	140	138	136	136	138	139	140	4	4.1	4	4.8	4.7	4.6	4	IV	iv	iv	250	180	212	28	38	35	45	38	39	52
97	ARB	AS	1	0.6	0.9	1	1.2	146	144	140	138	141	142	143	5	4.1	4.4	4.2	3.7	4.9	5	II	III	III	302	280	298	30	48	45	46	34	39	67
98	ARNI	AK	0.8	1	0.8	0.8	0.7	133	127	124	135	130	128	132	4	5.5	4.6	4.1	5	5.3	5	II	II	II	318	324	400	42	30	40	30	43	40	50
99	ARNI	MS	0.5	0.4	0.9	0.8	1	143	140	135	128	137	138	137	5.3	3.6	4	3.7	4.1	3.8	3.8	III	II	II	240	270	390	20	30	38	48	45	40	64
100	ARB	NK	0.8	1.3	1	1.2	1	140	138	136	140	138	129	140	5.1	3.8	4.6	5.1	4.9	5	4.9	II	II	II	360	346	340	32	35	33	40	43	44	53

Sr. No	Group	Name	ECHO PARAMETERS																	DOSE OF ARNI	HOSP 6M	HOSP 6-12M	MORT 6M	MORT 6-12M	ADVERSE EVENTS					Loss to follow up
			LVIDd		LA-DIAMETER			MV E/A			MR SEVERITY			PASP			TAPSE													
			6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR	BASELINE	6 MONTHS	1 YEAR						SYMP. HYPOTN	DEC. RENAL FN	K>5.5	ANGIOEDEMA	OTHER	
81	ARB	RK	49	48	33	35	36	1.6	1.5	1.6	mod	mod	mod	50	55	40	18	23	21	-	-	-	-	-	-	-	-	-	-	-
82	ARB	HK	78	78	51	53	50	1.5	1.6	1.6	no	mild	mod	30	32	36	16	20	18	-	-	-	-	-	-	-	-	-	-	-
83	ARB	GS	53	55	31	33	35	0.8	0.9	1	no	no	no	20	28	30	20	23	22	-	-	-	-	-	-	-	-	-	-	-
84	ARB	HK	65	66	43	45	46	0.7	0.8	0.8	mild	mod	mild	20	40	42	21	24	23	-	-	Y	-	-	-	-	-	-	-	-
85	ARB	KL	62	61	48	50	48	1.2	2.1	1.2	mod	mod	mod	38	45	48	12	12	16	-	-	-	-	-	-	-	-	-	-	-
86	ARB	PP	73	72	50	53	48	1.3	1.5	1.2	mod	sev	sev	64	65	46	24	22	20	-	-	Y	-	-	-	-	-	-	-	-
87	ARB	KD	53	52	30	32	35	1.2	1.4	1.5	mild	mild	NO	25	29	32	22	21	20	-	-	-	-	-	-	-	-	-	-	-
88	ARB	SS	68	68	42	40	42	0.8	0.6	0.9	sev	NO	NO	64	20	24	24	23	23	-	-	-	-	-	-	-	-	-	-	-
89	ARB	UM	49	50	33	50	40	0.8	0.8	0.7	no	no	NO	35	27	30	20	22	21	-	-	-	-	-	-	-	-	-	-	-
90	ARB	KK	58	59	37	38	36	0.8	0.7	0.8	mild	mild	mild	34	35	38	24	18	23	-	-	-	-	-	-	-	-	-	-	-
91	ARB	K	56	55	30	30	32	1.2	1.4	1.2	mild	mod	mod	40	48	36	25	23	23	-	-	-	-	-	-	-	-	-	-	-
92	ARNI	LK	80	70	40	45	35	1.2	0.7	1.1	mild	mod	mild	27	40	40	24	20	20	100	Y	-	-	-	-	-	-	-	-	-
93	ARNI	M	75	70	59	60	50	1.6	1.7	1.3	mild	mod	mild	30	48	45	14	14	20	100	-	-	-	-	-	-	-	-	-	-
94	ARB	UJ	49	48	41	43	38	0.8	0.8	1	no	no	mild	22	28	25	22	21	20	-	-	-	-	-	-	-	-	-	-	-
95	ARNI	DS	50	48	42	40	37	0.9	0.6	0.8	mild	mild	NO	24	35	32	24	24	25	100	-	-	-	-	-	-	-	-	-	-
96	ARB	RR	48	50	28	38	41	1.1	1.1	1.1	no	no	NO	25	11	20	15	18	17	-	-	-	-	-	-	-	-	-	-	-
97	ARB	AS	40	42	34	44	38	1.4	1.3	1.3	no	no	NO	23	30	24	24	22	21	-	-	-	-	-	-	-	-	-	-	-
98	ARNI	AK	58	48	51	38	36	ONLY E	ONLY E	ONLY E	mod	mild	NO	60	50	42	28	29	30	100	Y	-	-	-	-	-	-	-	-	-
99	ARNI	MS	54	50	48	48	36	0.8	0.7	0.9	mod	mild	NO	60	45	42	10	9	18	100	-	-	-	-	-	-	-	-	-	-
100	ARB	NK	52	53	52	51	48	1.5	1.4	1.2	sev	sev	sev	34	35	22	23	22	20	-	-	Y	-	-	-	-	-	-	-	-

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The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Ashish Kumar**, a student of your college for **DM Cardiology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Assessment of clinical and echocardiographic features in systolic heart failure patients switched from angiotensin receptor blockers to sacubitril/valsartan

Supervisor
Dr. Gurpreet S. Wander
Prof. & Head,
Dept .of Cardiology,
DMCH, Ludhiana.

Co-Supervisor
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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

Doctorate of Medicine

In

Cardiology

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

APRIL, 2019

DR ASHISH KUMAR

DEPARTMENT OF CARDIOLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN
For the degree of	D.M Cardiology
Name of the candidate	Dr Ashish Kumar
Supervisor	Dr. Gurpreet S Wander, Professor & Head, Department of Cardiology, DMCH, Ludhiana
Co-supervisor	Dr. Abhishek Goyal, Associate Professor, Department of Cardiology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)] which have been shown to improve survival in patients with HFrEF.

Aim of Study: To access effects of SACUBITRIL/VALSARTAN therapy on clinical parameters and echocardiographic features in HFrEF patients as compared to angiotensin receptor blockers.

Materials & Methods: The study will be performed on 100 patients with HFrEF who are already on ARBs in addition to optimal medical therapy.

Clinical Significance: This study will determine Sacubitril/Valsartan effects on LVEF and remodeling beyond the effects of concomitant optimal medical therapy.

Keywords: Sacubitril/Valsartan, HFrEF, NYHA, angiotensin receptor blockers.

(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN"** exist in the Department of Cardiology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

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Date : 11-4-2019

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Ashish Kumar
Department	Cardiology
Topic of Thesis	ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN
Likely date of appearing in PG examination	May 2021
Date of enrollment	27 Aug,2018
Name of Head of Department	Dr. Gurpreet S Wander
1) Supervisor **2) Co-Supervisor(s)**	Dr. Gurpreet S Wander Dr. Abhishek Goyal
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
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	9. Secretary, IEC
	10. Dean Academics
	11. Vice Principal
	12. Principal

Approved: Yes / No

Chairperson
Research Committee

Approved: Yes / No

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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4	DATE OF ADMISSION OF COURSE	27 AUGUST 2018
5	TITLE OF THE TOPIC	ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN

6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Heart failure (HF) is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or the ejection of blood. The most common cause for HF is reduced left ventricular myocardial function; however, dysfunction of the pericardium, myocardium, endocardium, heart valves or great vessels alone or in combination is also associated with HF. Some of the major pathogenic mechanisms leading to HF are increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neuro-humoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis and genetic mutations.[1]

The main terminology used to describe HF is historical and is based on measurement of the LVEF. HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40–49% represent a 'grey area', which we now define as HFmrEF. Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies.[2]

The burden of cardiovascular disease is increasing in India. Estimates based both on data of established risk factors for heart failure (HF) as well as small studies suggest that the burden of HF in India is not <2-5 million patients [3] with an estimated prevalence of 2–3/1000 population. Results from clinical trials show that in-hospital mortality associated with cardiovascular disease is

higher in India than in Western nations. Mortality rates due to myocardial infarction have been reported as high as 16.7% in Indian hospitals,[4] compared with rates of 4–7% in Western hospitals.[5-7]

Neuro-hormonal antagonists (ACEIs or ARBs, MRAs and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (SACUBITRIL/VALSARTAN)]. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin. The degradation of NPs, bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy.[8] The new joint guidelines from the American College of Cardiology, American Heart Association, and Heart Failure Society of America recommend sacubitril/valsartan for patients with HFrEF who have symptoms that meet New York Heart Association class II or III heart failure and can tolerate an ACE inhibitor or ARB. Even further, these guidelines recommend replacing ACE inhibitor or ARB therapy with sacubitril/valsartan in patients with adequate blood pressure for morbidity and mortality benefit.[9]

Oral bioavailability of LCZ696 is >=60%.Steady-state is reached in 3 days. It is highly protein bound 94-97%.Volume of distribution is 75 L for sacubitril and 103 L for valsartan. Sacubitril component is primarily excreted in the urine (52-68%) and feces (37-48%). Valsartan component is primarily excreted in the feces (86%) and to a lesser extent in the urine (13%). Despite the superiority of sacubitril/valsartan over enalapril in the PARADIGM-HF trial, some relevant safety issues remain when initiating therapy with this drug in clinical practice. Symptomatic hypotension was more often present in the sacubitril/valsartan group although there was no increase in the rate of discontinuation. Sacubitril/valsartan tends to increase risk of angioedema. If angioedema occurs, LCZ696 (sacubitril/valsartan) should be discontinued and should NOT be rechallenged. LCZ696 (sacubitril/valsartan) should not be used in those with a history of angioedema related to previous ACE inhibitor or ARB therapy. If switching to or from an ACEi or ARB, a 36-hour washout period is required between drugs. Combined treatment with an ACEI (or ARB) and sacubitril/valsartan is contraindicated. Being a RAAS blocking agent; LCZ696 (sacubitril/valsartan) may cause impaired renal function in high risk individuals including those with renal artery stenosis. Because of RAAS blockade, sacubitril/valsartan may cause hyperkalemia. There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition.[10]

6.2 REVIEW OF LITERATURE

Yasunori Suematsu et al in year 2016 evaluated the effects and mechanisms of SACUBITRIL/VALSARTAN in HF with reduced ejection fraction (HF-rEF) in streptozotocin-induced diabetic mice and concluded that the SACUBITRIL/VALSARTAN LCZ696 improved cardiac function with the reduction of fibrosis in an HF-rEF model in diabetic mice, by suppressing TGF-β. This effect may be due to the specific inhibition of neprilysin, beyond the ARB effect of LCZ696.[11]

A study was conducted by R. De Vecchis et al in year 2017 which was a retrospective cohort study aimed to assess the effects of sacubitril/valsartan in addition to a beta-blocker and mineral receptor antagonist (MRA) in a group of HFREF patients with NYHA class II-III HF vs. conventional therapy (ACE inhibitor or angiotensin II receptor blocker added to a beta-blocker plus an MRA) administered to a control group of HFREF patients with comparable clinical features. In both groups, treatment was supplemented by a loop diuretic, usually furosemide, at variable doses. Mortality at 6 months was 6.8% in patients taking sacubitril/valsartan vs. 34% in those on conventional therapy (odds ratio [OR] = 0.14; 95% CI: 0.04-0.49). Moreover, there was a 4.5% rate of HF hospitalizations in the sacubitril/valsartan group vs. 59% in the control group (OR = 0.03; 95% CI: 0.01-0.14). It was concluded that Sacubitril/valsartan offered strong protection against all-cause death and HF hospitalizations at 6 months without any significant side effects.[12]

Aws Almufleh et al in year 2017 performed a single center, retrospective, cohort study of HFrEF patients (n=48) who were treated with Sacubitril/Valsartan for a median duration of 3 months (Interquartile range 2-6

months). Clinical and echocardiographic parameters were reviewed at three time points (pre-baseline which was median of 18 months before starting Sacubitril/Valsartan, baseline before treatment started, and post-Sacubitril/Valsartan). Sacubitril/Valsartan use was associated with an average 5% (±1.2) increase in EF, from a mean baseline of 25.33% to 30.14% ($p<0.001$) with a median duration of treatment 3 months. There was no significant change in mean LVEF over a median duration of 11 months (IQR 5.5-15.5) between pre-baseline and baseline time points prior to treatment ($p=1.0$). The mean increase in ejection fraction tended to be marginally greater in the medium/ high dose cohort as compared to the low dose cohort, with a mean increase of 5.09% (±1.36) and 4.03% (±3.17), respectively ($p=0.184$). There was a 3.36 mm reduction in left ventricular end-systolic diameter ($p=0.04$), a 2.64 mm reduction in left ventricular end-diastolic diameter ($p=0.02$), and a 14.4 g/m2 reduction in left ventricular mass index ($p<0.01$). It was concluded that Sacubitril/Valsartan was found to improve EF and multiple measures of reverse remodeling beyond the effects of concomitant optimal medical therapy.[13]

Biering-Sorensen in 2018 conducted a phase 2, randomized, parallel-group, double-blind multicenter trial in 301 patients with New York Heart Association (NYHA) class II-III HF, LVEF ≥45%, and NT-proBNP ≥400 pg/mL. Participants were randomly assigned (1:1) to sacubitril/ valsartan titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily for 36 weeks. Patients were assessed for change in GLS (global longitudinal strain) and GCS(global circumferential strain) from baseline to 36 weeks, adjusting for baseline value, in patients with sufficient imaging quality for 2D speckle tracking analysis at

both timepoints (n=60 S/V, 75 valsartan only). GCS was significantly improved at 36 weeks in the SACUBITRIL/VALSARTAN group when compared with the valsartan group (Δ 4.42, 95% CI 0.67- 8.17, p=0.021), with no significant difference observed in GLS (Δ0.25, 95% CI -1.19-1.70, p=0.73). It was concluded that in patients with HFpEF, S/V improved global circumferential but not longitudinal strain when compared to valsartan during a 36 weeks period.[14]

Wachter and colleagues in year 2018 randomly assigned 1,002 patients (mean age, 67 years; 75% men; mean left ventricular ejection fraction, 29%) hospitalized for acute decompensated HF with reduced EF to sacubitril/valsartan after being hemodynamically stabilized while still in the hospital or after discharge. Patients were also stratified by whether they were taking an ACE inhibitor, an angiotensin receptor blocker or neither before hospitalization. Of the cohort, 29% were newly diagnosed with HFrEF and 24% had not previously taken ACE inhibitors or angiotensin receptor blockers. The primary endpoint was proportion of patients achieving the target dose of sacubitril/valsartan 200 mg twice daily at 10 weeks after randomization. Secondary endpoints included discontinuation due to drug-related adverse events and tolerability of different sacubitril/valsartan doses. The primary endpoint was achieved in 45% of the predischarge group and 50.4% of the postdischarge group (relative risk ratio [RRR] = 0.893; 95% CI, 0.783-1.019). In addition, 62.5% of the predischarge group and 68% of the postdischarge group maintained a dose of 100 mg or 200 mg for at least 2 weeks leading to week 10 after randomization (RRR = 0.919; 95% CI, 0.839-1.008), whereas 86.4% of the predischarge group and 88.8% of the postdischarge group

maintained any dose for at least 2 weeks leading to week 10 after randomization (RRR = 0.973; 95% CI, 0.929-1.02).Study drug discontinuation occurred in 4.5% of the predischarge group and 3.5% of the postdischarge group (RRR = 1.287; 95% CI, 0.692-2.395).Rates of adverse events, serious adverse events and death did not significantly differ between the groups. Death rates were low and none were related to the study drug. The most important finding is that it is as safe and efficacious to start sacubitril/valsartan in the hospital as in the outpatient setting, whether the patient is on a high dose or a medium dose of the drug.[15]

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To study clinical and echocardiographic features in systolic heart failure patients on Angiotensin receptor blockers.
2. Assessment of clinical and echocardiographic features when patients were switched over from Angiotensin receptor blockers to SACUBITRIL/VALSARTAN therapy and comparison between two groups.

7.0 MATERIALS AND METHODS

The study population will consist of 100 patients with HFrEF who are already on ARBs (valsartan/losartan) in addition to optimal medical therapy in DMC & HOSPITAL.

These patients will be analysed at baseline by NYHA FUNCTIONAL CLASS, 6 minute walk test and transthoracic echocardiography. Imaging data will be analysed for LV dimensions and volume.

These patients will be followed up for 6 months and reassessed for NYHA FUNCTIONAL CLASS, 6 minute walk test and transthoracic echocardiography.

Thereafter patients will be given option for SACUBITRIL/VALSARTAN combination and those who will opt will be switched over from ARBs to SACUBITRIL/VALSARTAN on maximum tolerated dose. All patients will be followed up for additional six months and reassessed for NYHA class, 6 minute walk test and TTE.

At the end of 1 year comparison will be made between patients who were switched over to SACUBITRIL/VALSARTAN versus patients who continued ARBs.

Also comparison will be made between the clinical parameters and echocardiographic features at 6 months versus at 1 year.

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina.[16]

The six-minute walk test is a simple, inexpensive, and reproducible method for the assessment of exercise capacity. During the test, the patient walks the longest possible distance within the time of 6 minutes on the flat surface and can stop or slow down at any time and then resume walking during the test. The main result of the six-minute walk test (6MWT) is the distance covered by the patient in 6 minutes. The 6MWT shows good correlation with the peak VO2 from cardiopulmonary exercise test and is much easier to perform, and it reflects well the daily activities of the patients.[17]

TTE will be used for measurement of LV dimensions and volume. The most commonly used 2D method for volume measurements is the biplane method of discs (modified simpson's rule).[16] The principle underlying this method is that the total LV volume is calculated from the summation of a stack of elliptical disks. LV volumes will be measured from apical 4 and/or apical 2 chamber views, tracing the endocardial border of the LV. If there is no wall motion abnormality, the EF can be estimated from one view only, apical 4 chamber or apical 2 chamber view. The ejection fraction is calculated from the difference between end-diastolic and end-systolic LV volume, divided by the end-diastolic LV volume:

$$EF = \frac{\text{End-diastolic volume - end-systolic volume}}{\text{end-diastolic volume}}$$

7.1 SOURCE OF DATA

Data collection will be done by analyzing the patients with HFrEF enrolled from DMC & HOSPITAL at baseline, 6 months and 1 year.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA: Patients with HFrEF (EF<40%).

EXCLUSION CRITERIA: 1.Symptomatic hypotension.

2. An estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area.

3. Serum potassium level of more than 5.5 mmol per liter.

4. History of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs.

OUTCOME: It is hypothesized that SACUBITRIL/VALSARTAN will improve clinical profile and echocardiographic parameters beyond the effects of concomitant optimal medical therapy.

STATISTICAL ANALYSIS: After data has been collected, it will be subjected to analysis using appropriate statistical methods. The data obtained at various stages of the study will be compared taking into account the specific objectives of the study.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

NO

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

ATTACHED HEREWITH

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PROFORMA

Name: GROUP:

Age:

Sex:

MRD No.:

Address:

Chief complaints:

Brief History of Present:

Illness

Past History

DIABETES MELLITUS:

HYPERTENSION:

CKD:

Personal History

Smoker/Non Smoker:

Alcoholic/Non-Alcoholic:

Veg. / non veg:

Medications at baseline:

Signature of Candidate Signature of Supervisor

Family History

Diabetes Mellitus:

Hypertension:

Examination

GPE

Height:

Weight:

Anemia :

Cyanosis :

Jaundice :

Oedema :

JVP-

Pulse :

Blood Pressure :

Respiratory Rate:

Temperature :

System Examination

-Abdomen

-CVS:

-Chest:

-CNS:

Investigations

CBC

FBS/RBS

BNP

ECG

RFT every 2months

Signature of Candidate

Signature of Supervisor

	Baseline	2 months	4 months	6 months	8 months	10 months	12 months
Na							
K							
Cl							
Urea							
Creat							

	Baseline	6 months	1 year
NYHA Class			
6 Minute walk distance			
ECHO Parameters: LV EJECTION FRACTION LV Internal Diameter(systole) LV Internal Diameter(diastole) LA Diameter MV E/A velocity ratio Mitral regurgitation severity PASP TAPSE			

Maximum Tolerated Dose of sacubitril/valsartan:

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ANGIOTENSIN RECEPTOR BLOCKERS TO SACUBITRIL/VALSARTAN" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ